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CONTENTS

ORIGINAL ARTICLES:

Effect of Apnea Neonatorum on Intellectual Development—*Gene L. Usdin, M.D., and Marvin L. Weil, M.D.* 387

Unipolar Lead Electrocardiography in Children with Special Reference to Its Value in Congenital Heart Disease—*L. George Veasy, M.D., and Forrest H. Adams, M.D.* 395

Q-T Interval During Active and Inactive Rheumatic Fever—*Sidney Finkel, M.D., and Janet S. Baldwin, M.D.* 410

Sulfobromophthalein Sodium Excretion Test as a Measure of Liver Function in Premature Infants—*William Obrinsky, M.D., Malcolm L. Denley, M.D., and Ralph W. Brauer, Ph.D., with the technical assistance of Rita Pessotti, B.S., and Marilyn Hughes, B.S.* 421

Report of Two Years' Experience in the Transportation of Premature Infants in New York City—*Helen M. Wallace, M.D., Margaret A. Losty, R.N., and Leona Baumgartner, M.D.* 439

Duplications of the Alimentary Tract—*Robert E. Gross, M.D., George W. Holcomb, Jr., M.D., and Sidney Farber, M.D.* 449

Studies on Abnormal Hemoglobins. IV. Persistence of Fetal Hemoglobin in the Erythrocytes of Normal Children—*Amoz I. Chernoff, M.D., and Karl Singer, M.D.* 469

(Contents continued on page iv)

CONTENTS

(Contents continued from page iii)

Adrenal Cortical Hyperfunction in Childhood; Report of a Case with Adrenocortical Hyperplasia and Testicular Adrenal Rests—*Elizabeth Kirk Rose, M.D., Horatio T. Enterline, M.D., Jonathan E. Rhoads, M.D., and Edward Rose, M.D.* 475

Effects of Early Feeding of Strained Meat to Prematurely Born Infants—*M. B. Andelman, M.D., P. S. Gerald, M.D., A. C. Rambar, M.D., and B. M. Kagan, M.D.* 485

AMERICAN ACADEMY OF PEDIATRICS:

The President's Page—*Warren W. Quillian, M.D., President* 492

Round Table Discussion: Metabolic Diseases in Children—*Victor A. Najjar, M.D., Chairman* 494

Symposium on Carbohydrate Metabolism—*Charles H. Best, M.D., Chairman*... 501

SPECIAL SECTIONS:

The Pediatrician and the Public—*Paul A. Harper, M.D., Editor.* Maternity and Infant Care for Military Dependents; an Official Statement Adopted by the Executive Board, American Public Health Association, Inc. 508

TRENDS—*John P. Hubbard, M.D., Contributing Editor.* Practice of Preventive Pediatric Care 513

Public Health, Nursing and Medical Social Work—*Myron E. Wegman, M.D., Contributing Editor.* Current Status of Birth, Death and Infant Mortality Rates ... 515

Correspondence 517

News and Announcements 518

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Pediatrics

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ORIGINAL ARTICLES

EFFECT OF APNEA NEONATORUM ON INTELLECTUAL DEVELOPMENT

By GENE L. USDIN, M.D.,* AND MARVIN L. WEIL, M.D.
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THE question of the ultimate effect of varying degrees of delayed onset of respiration in the newborn infant has always been troublesome to the physician. Studies, mainly done in the past 13 years, have led to conflicting conclusions. There are those who claim that temporary cerebral changes will take place if the infant does not breathe spontaneously within 30 seconds after the cord is severed,[1, 2] and that permanent cerebral changes will ensue if oxygenation of the blood stream does not occur within one or two minutes.[2, 3] On the other hand, others are not convinced that damage leading to subsequent ill-effects need necessarily occur when the infant does not breathe within the first few minutes.[4–6] The present study was designed to compare the intellectual development, at 13 or 14 years of age, of children who had been apneic at birth with that of children who had breathed spontaneously (see table 1).

In this problem, as always, nomenclature is of cardinal importance. The term asphyxia has had the widest use in connection with the problem. Dorland's *American Illustrated Medical Dictionary*[7] defines asphyxia as "suffocation, also suspended animation from suffocation." There are numerous shadings of and objections to this definition. Etymologically asphyxia means the absence of throbbing. Gradually the import of the word has centered more on suffocation. Eastman[8] points out that the term apnea neonatorum, which is merely descriptive and carries no implication with regard to etiology, seems preferable to the older designation. This paper utilizes the term apnea to define more clearly the state which the present authors studied. In quoting other studies, however, the term employed by the particular authors cited will be used.

The ability of fetal and newborn organisms to survive a period of neonatal apnea which would be fatal to an adult has been well established.[9, 10] Nevertheless there can be

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TABLE 1

Apneic Group				Control Group		
Child No.	Duration of Apnea	Grade in School	I.Q.	Child No.	Grade in School	I.Q.
1.	5	8	71	1.	6	58
2.	3	7	72	2.	SL	69
3.	4	SL*	73	3.	6	72
4.	10	5	75	4.	7	73
5.	10	SL	78	5.	8	73
6.	4	7	80	6.	7	74
7.	6	6	80	7.	6	79
8.	3	6	81	8.	7	81
9.	3	6	81	9.	6	82
10.	3	7	83	10.	8	83
11.	3	6	86	11.	8	84
12.	7	6	86	12.	6	85
13.	10	7	87	13.	7	86
14.	4	7	89	14.	8	88
15.	3	6	89	15.	7	89
16.	4	8	92	16.	7	89
17.	3	8	93	17.	7	89
18.	5	6	95	18.	7	90
19.	4	7	95	19.	7	90
20.	3	7	96	20.	8	91
21.	3	7	97	21.	6	92
22.	3	7	97	22.	7	93
23.	5	8	98	23.	7	93
24.	3	8	98	24.	7	95
25.	6	6	101	25.	7	95
26.	6	8	101	26.	8	96
27.	3	7	101	27.	7	96
28.	3	7	102	28.	7	96
29.	3	8	102	29.	8	97
30.	4	8	103	30.	8	98
31.	10	7	105	31.	8	98
32.	4	8	106	32.	7	98
33.	3	8	107	33.	7	100
34.	3	8	108	34.	8	105
35.	6	7	110	35.	7	107
36.	3	7	113	36.	8	108
37.	3	8	114	37.	8	108
38.	5	8	118	38.	8	109
39.	4	8	123	39.	8	111
40.	5	8	130	40.	8	111
41.	5	8	130	41.	7	117
				42.	8	122
				43.	8	129

* Slow learner class.

no doubt that there is a period of neonatal apnea which cannot be exceeded without increased likelihood of permanent physical or mental impairment.

Courville[11] has emphasized that the principal and most important effects of anoxemia are to be found in the central nervous system, and this is due to the sensitive character of nervous tissue. Over 40 years ago, Gomez and Pike[12] noted that the cells of the cerebrum suffered permanent damage after eight minutes of anoxia, that the Purkinje cells of the cerebellum showed diffuse chromatolysis after 13 minutes, and that the cells of the vital medullary centers showed similar results after 20 to 30 minutes. More recently, Weinberger and his co-workers[13] confirmed the observation that the cerebral cortex is the first area involved. Thus oxygen deficiency can injure the cortex without affecting the vital centers. The important question that remains unanswered, however, is the degree of anoxia necessary to produce permanent damage or destruction of cortical cells. Investigators, working with laboratory animals, have made various estimates regarding the length of time that cortical cells can tolerate circulatory arrest; their estimates have ranged from 3 minutes 10 seconds[13] to 7 or 8 minutes[12, 14] and "less than 10 minutes."[15]

The majority of studies concerning effects of neonatal apnea have been done retrospectively. A group of persons known to have some physical or mental defect was selected, and an attempt was made to secure birth histories of the group; finally the percentage of apneic infants in the defective group was compared to that found by a study of routine deliveries. Such studies may give suggestive evidence but do not provide for prognostic assessment of apneic infants. Obviously, the apneic infants who showed normal development would not have been followed by this technic.

Schreiber[16] noted that 70% of 500 children referred because of neurologic disorders had a history of apnea at or soon after birth; but, in evaluating this finding, we must consider the possibility that the apnea in some patients might have been on the basis of a congenital neurologic disorder. In a later paper, Schreiber[17] reported an investigation of 146 children who had low intelligence quotients. He included only those whose birth histories were available from hospital records. He excluded 46 of the original 146 because of a family history of mental deficiency or postnatal factors, and compared the remaining 100 with 100 control children of comparable background but of "good adjustment." The criteria for apnea were not given; and whereas individual tests of intelligence were done on the retarded children, group intelligence ratings were used for the controls. His article did not specify the names of the individual or group tests used. Cronbach[18] has emphasized that "different tests of the same function are not interchangeable" and that a number of authors have not only used different groups for standardization but often have converted simply on the basis of the mean being 100. Also the inferiority of group intelligence tests as contrasted with individual tests is well established.[19] The discrepancy between results of group tests and true intelligence may be sufficiently large to suggest apparent differences of considerable proportions, and yet the differences may really be insignificant. By such a retrospective technic, Schreiber concluded that a relationship existed between low intelligence and neonatal apnea from whatever cause.

In recent years a number of reports have traced the development of children known to have been apneic or asphyxiated at birth. McPhail and Hall[20] analyzed a series of 1,005 deliveries and found "severe apnea" to be present in 5.8% and "mild apnea" in 8.7% of the cases. Those cases considered as fulfilling the criteria for severe apnea were "all cases in which breathing and crying were delayed more than a minute and all cases

developing cyanosis in the first few days of life." Cases considered as fulfilling the criteria for mild apnea were those "in which the onset of respiration was delayed more than thirty seconds but was well established in one minute; in this latter category if cyanosis was present it must have cleared as breathing became regular." The authors attempted a follow-up at school age of 861 consecutively born infants and were able to trace 270 of them. Of these, 23 had had "mild apnea" at birth while only 11 had experienced "severe apnea." The children were given group intelligence tests (Kuhlmann-Anderson), and teachers completed the Haggerty-Olsen-Wickham Behavior Rating Schedules on their individual students. McPhail and Hall concluded that apnea may be present at birth without resultant brain damage provided that oxygen is given during the apneic period. The following factors must be considered in evaluating this conclusion: (1) the apnea was of shorter duration than that studied by most subsequent investigators; (2) cyanosis was used as one of the criteria; (3) group intelligence quotient tests were used.

The implications of the first factor are immediately evident, and the third has been discussed previously. Since cyanosis is dependent upon adequacy of oxygenation of the red blood cells, infants with elevated red blood cell counts may show cyanosis without having any oxygen want on the part of tissues.[21, 22] The high degree of unsaturation of fetal blood in respect to oxygen indicates that the full-term fetus in utero exists normally in a state of cyanosis.[23]

From a study of 25,261 deliveries, Darke[24] selected 49 cases in which the infant had survived a severe degree of anoxia without obvious accompanying physical trauma. His criteria for selection were: (1) no abnormal neurologic findings at the time of birth, during the neonatal period, or at the time of the follow-up examination; (2) severe asphyxiation, with an effort being made to secure cases of children who had asphyxia pallida or who were definitely stated to have been apneic for a period of three minutes or longer; (3) cases in which intracranial hemorrhage was neither diagnosed nor suspected. Darke was able to trace 19 of the 49 children and to have psychologists administer Stanford-Binet Intelligence Tests to them. As a control, a parent or sibling of each asphyxiated child was examined. Darke concluded that "very severely asphyxiated and apneic newborn infants with no evidence of injury at or following birth are significantly retarded in mental development."

Difficulties encountered by Darke in his study may have affected his conclusion. Four of his subjects met one of the criteria by inference from birth histories, while in an additional group of five children no objective statement as to duration of apnea was obtainable. The age of the children at the time of the follow-up examination varied from 2 years and 5 months to 11 years and 8 months. Green[25] has noted that pre-school tests correlate poorly with Stanford-Binet tests given in later years and actually tests given at 2½ years have a correlation of but 0.39 with those given at the age of seven years. Darke evaluated the validity of his control group by noting that the correlation between intelligence of parents and their children in the general population has been reported to range from 0.45 to 0.55[26] and the coefficient of correlation between intelligence of siblings on the Stanford-Binet scale was reported to range between 0.40 and 0.68.[27] This degree of correlation cannot be considered high.

Campbell and his co-workers[5] have recently completed a detailed and thorough study of the effects of asphyxia neonatorum. Their criteria for selection of the asphyxiated group were: (1) asphyxia pallida; (2) asphyxia livida lasting for a period of over two minutes.

As a control group, children born immediately before and immediately after each "asphyxia" patient were used. Sixty-one of the "asphyxia" group and 133 of the control group were given the Raven Progressive Matrices Intelligence Tests. This test divides subjects into five grades. The Raven Matrices showed no significant difference in the intelligence distribution of the two groups. In a discussion of the Matrices, Raven[28] emphasized that it is not a test of general intelligence but is a "non-verbal test of a person's capacity at the time of the test to apprehend figures presented for his perception, see the relations between them and conceive the correlative figures completing the systems of relations presented." Thus, rather than testing the combinations of factors making for intelligence, Raven's Progressive Matrices seem to be primarily a test of integrative capacities combining perceptual and conceptual abilities. Also the Progressive Matrices are comparatively recent in origin, apparently have been used primarily in Great Britain, and therefore lack the thorough standardization of the Stanford-Binet tests.

In the present study a case was excluded from consideration if any of the following conditions were present: (1) prematurity of more than a month; (2) delivery by cesarean section; (3) any abnormal neurologic finding at the time of birth, during the neonatal period or at the time of the present examination; (4) diagnosis or even suspicion of intracranial hemorrhage; (5) history or evidence of any hereditary or congenital factor or of obvious neurologic lesion attributable to the delivery or to subsequent trauma that in itself might impair the infant's development. Thus a history of head trauma, brain infection, congenital heart disease, hemorrhagic disease of the newborn, positive serologic reaction of the mother during pregnancy, rubeola in the first trimester of the pregnancy, or familial feeblemindedness excluded the cases from the study. Technics of resuscitation used on the apneic infants were aspiration of mucus, oxygen by mask, mouth-to-mouth breathing, water baths and intramuscular injections of stimulating drugs.

The records of 2,432 obstetric cases, representing all the births at the Cincinnati General Hospital during 1937, were reviewed. From these were selected all cases of infants who were apneic for three or more minutes and who fulfilled the aforementioned criteria. Ninety such cases were found. As a control an equal number of cases of infants who breathed immediately at birth and who also fulfilled the above criteria were selected at random from births occurring during 1937. The records of the State Hospital for Feeblemindedness and Epilepsy were checked, and apparently none of these 180 children had been or were patients at these institutions. It was possible to locate 45 of the control and 43 of the apneic group. Subsequently two from each group were eliminated on the basis of further medical data in the charts of the Children's Hospital and the Cincinnati General Hospital. The school health records of the remaining 43 children in the control and the 41 in the apneic group were reviewed, and each child was given a physical and neurologic examination without the examiner's knowing the birth history of the child being examined. No further exclusions were necessary on this basis. Then the Stanford-Binet, Form L, Intelligence Test was administered to each child without the psychologist's knowing to which group the child belonged. Four children in each group who had taken this test within the past four years were not tested.

Results

Evaluation of intelligence by Stanford-Binet tests revealed a normal distribution for the intelligence of the apneic group around a mean quotient of 96.2, whereas that of the control group was normally distributed around a mean of 93.0. The range of intelligence

quotients of the apneic group was from 71 to 130, whereas that of the controls was from 69 (with the exception of a 58 which was substantially separated from the other scores) to 129. Particularly noteworthy is the fact that one child who had a 10 minute apneic period at birth had an intelligence quotient of 105 fourteen years later. Two children who had experienced five minute periods of neonatal apnea had the highest intelligence quotients (130) of all the children studied. Also the mean intelligence quotient of the 17 children who had had 4, 5 or 6 minute periods of apnea was 99.7.

Computation of the standard error of the mean revealed the lack of a significant difference between the apneic and control groups:

Group	No.	Mean I.Q. ± S.E. of the mean
Apneic	41	96.2 ± 2.34
Control	43	93.0 ± 2.20

As a confirmatory statistical procedure, Student's T-test[29] was used, and this revealed no significant difference between the means of the two groups. The probability of the occurrence of a difference as great as or greater than that between these means was found to be 0.32.

Summary

The intelligence of a group of 41 children who had been apneic for three or more minutes at birth was compared with that of a control group of 43 children who had breathed spontaneously at birth. The children were 13 and 14 years old at the time of the study. All the children had been born in the Cincinnati General Hospital in 1937 and therefore should derive from an essentially similar socio-economic strata. Insofar as seemed possible, all cases with factors that might in themselves have impaired the child's motor or intellectual development were excluded. Individual intelligence tests were administered. A statistical analysis of the results of these tests revealed no significant difference between the intelligence of the apneic and control group.

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SPANISH ABSTRACT

Efectos de la Apnea del Recien Nacido Sobre el Desarrollo Intelectual

El problema del efecto real que pueden ocasionar diversos grados de retraso en la iniciación de la respiración en el recién nacido, ha constituido siempre una interrogación para el médico.

Los estudios, principalmente hechos en los últimos 13 años, han llevado a conclusiones contradictorias. Hay algunos que opinan que se presentarán cambios cerebrales transitorios si el niño no respira espontáneamente 30 segundos después de que el cordón umbilical ha sido seccionado, y que habrá alteraciones cerebrales permanentes si no hay oxigenación de la corriente sanguínea en uno ó dos minutos. Por otra parte ciertos autores no están convencidos de que ocurra necesariamente algún trastorno cuando el niño no respira en los primeros minutos de vida. El presente trabajo fué planeado para comparar el desarrollo intelectual a los 13 ó 14 años de edad, de los niños apnéicos al nacimiento con otros que habían respirado espontáneamente.

Se excluyeron aquellos casos que presentaban cualquiera de los siguientes problemas: (1) prematurez de más de un mes; (2) parto por sección cesarea; (3) cualquiera anomalía neurológica demostrada al nacimiento durante el período neonatal o al ser examinado para el presente estudio; (4) diagnóstico o aún sospecha de hemorragia intracraneana; (5) antecedentes o evidencia de cualquier factor hereditario o congénito o de lesión neurológica obvia, atribuible al parto o a un trauma subsecuente, que por sí misma comprometiera el desarrollo del niño. Así aquellos pacientes con historia de trauma craneano, infección cerebral, cardiopatía congénita, enfermedad hemorrágica

del recién nacido, reacciones serológicas positivas de la madre durante el embarazo, sarampión en el primer trimestre del embarazo o debilidad mental familiar, fueron desechados.

Se revisaron las historias clínicas de 2.432 casos obstétricos que representaban todos los nacimientos en el Hospital General de Cincinnati durante 1937. De estos se seleccionaron todos los niños que estuvieron apnéicos por tres ó mas minutos y que llenaron el criterio antes mencionado. Se encontraron 90 de estos enfermos. Como control se escogió un número igual de pacientes que respiraron inmediatamente al nacimiento y que también llenaron las limitaciones mencionadas, separándolos al azar de entre los nacidos en 1937. Fué posible localizar 45 de los controles y 43 del grupo apnéico, eliminando posteriormente 2 más de cada sección y quedando 43 niños en grupo de control y 41 en el apnéico. A todos los niños se les verificó un examen físico y neurológico sin que el médico que recogía los datos supiera la historia neonatal del niño examinado. La prueba de inteligencia de Stanford-Binet, Forma L, fué aplicada a cada uno, estando el psicólogo en conocimiento de cual era el grupo al que el niño pertenecía. Un análisis estadístico de los resultados de estas pruebas demostraron que no existían diferencias importantes entre la inteligencia del grupo apnéico y el de control. Teniendo un coeficiente de inteligencia medio para el grupo apnéico de 96.2 mientras que el grupo control lo tenía de 93.0 El margen de variación de los coeficientes para el grupo apnéico fué de 71 a 130, mientras que en los controles osciló entre 69 a 129.

1430 Tulane Avenue

UNIPOLAR LEAD ELECTROCARDIOGRAPHY IN CHILDREN

With Special Reference to Its Value in Congenital Heart Disease

By L. GEORGE VEASY, M.D.,* AND FORREST H. ADAMS, M.D.
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IT IS the authors' opinion, undoubtedly shared by others, that the electrocardiographic tracings taken by the standard leads fail too often to supply the specific information desired. This is particularly true in congenital heart disease. It is a distressing experience to find normal standard lead tracings in "left sided congenital heart lesions" (i.e., patent ductus arteriosus, subaortic stenosis, and coarctation of the aorta) which do not vary appreciably from tracings of "right sided congenital heart lesions" (i.e., interventricular defect, some cases of interatrial defect, and a few cases of isolated pulmonic stenosis).

Since an accurate anatomic diagnosis in congenital heart disease so often rests upon the confirmation of hypertrophy of a given chamber, and since it is obvious that standard leads are of limited value, it is strange that the method of unipolar lead electrocardiography has not been more widely studied. Although it has been over two years since Sokolow and Lyon[1, 2] first presented their criteria for ventricular hypertrophy with unipolar "V" leads, there has been a striking paucity of articles in the pediatric literature on this subject.[3, 4]

It was in the hope that the work of Sokolow and Lyon could be confirmed and that more accurate electrocardiographic criteria could be established that the standard limb leads and unipolar limb and precordial leads were analyzed in 72 cases of congenital heart disease in which the anatomic lesions were confirmed either by heart catheterization, operation, or postmortem study. In addition a series of 50 control cases of children with normal hearts was studied in the same manner. These normal children were divided into five equal groups from the following age groups: 1 to 6 months, 6 months to 2 years, 2 to 6 years, 6 to 10 years and 10 to 16 years.

BACKGROUND INFORMATION

Generally speaking, pediatricians are quite unfamiliar with unipolar lead electrocardiography. There is a tendency to regard it as a more complex form of electrocardiographic recording because of the greater number of leads taken. Actually, just the converse is true, for the standard leads are bipolar leads and therefore represent the difference in potential of two unipolar leads. For example, lead I is the recording of the electric activity of the heart which is picked up by the left arm electrode minus that electric potential which is picked up by the right arm electrode. Lead II tracings represent the recording of potential picked up by left leg electrode minus that of the right arm electrode. Lead III is the left leg minus the left arm.

It is easy to conceive the myriad ways by which any single tracing pattern could result. For example, a T-wave of a height of 5 mm. in lead I could be obtained by either of the two examples as seen in figure 1.

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Rather than having two electrodes roughly equidistant from the heart and recording varying equivalent electric potential as is the case with the standard (bipolar) leads, the unipolar lead records only the actual electric activity at the site of application of the so-called exploring electrode. Absence of alteration of the electric potential picked up by the exploring electrode is made possible by means of what is termed an indifferent electrode which records none or a negligible amount of electric potential. The exploring and indifferent electrodes are connected to the recording galvanometer in such a fashion that the exploring electrode is the positive pole and the indifferent electrode is the negative, thus allowing for positive currents to be recorded by an upstroke on the tracing.

The indifferent electrode as used today was developed by Dr. F. N. Wilson of the University of Michigan who in 1934 along with his co-workers first described its use.[5] He devised the indifferent electrode by uniting the three limb electrodes to a common terminal interposing a resistance of 5000 ohms in each of the three connecting wires (Fig. 2).

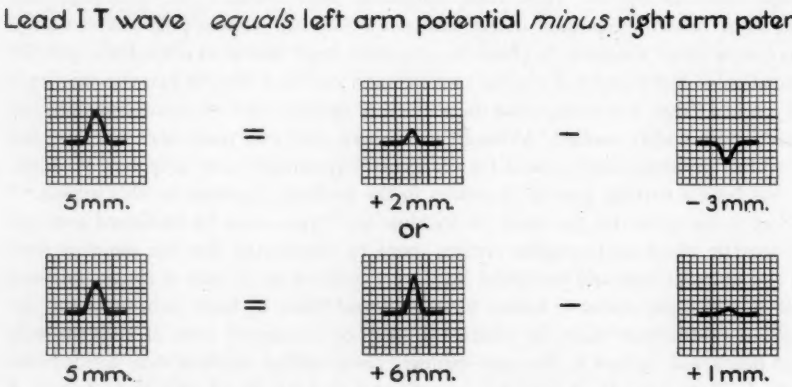


FIG. 1. Illustration showing how by standard lead electrocardiography T-wave in lead I of 5 mm. amplitude could be result of 2 entirely different electric situations.

The theory which prompted the creation of this electrode is the Einthoven triangle theory. This assumes that the heart is in the same plane and equidistant from the apices of an equilateral triangle represented by the three limb electrodes (Fig. 2). It is obvious that such an assumption is not entirely correct, but for practical purposes it has been well established that a V common electrode arising from these three points can be regarded as a truly indifferent electrode.

Goldberger in 1942 introduced a modification of the Wilson technic in that he eliminated the resistances and did not employ a connection to the indifferent terminal from the limb from which the tracing was being taken.[6] This technic, he claimed, gave tracings that did not vary significantly in patterns from those taken by the Wilson technic. In addition he claimed that these tracings were 1½ times as large as those taken by the Wilson technic and answered one of the criticisms of unipolar lead tracings.*

* Although the Goldberger technic was used in the present series, the authors wish to call to the reader's attention that there are authoritative differences of opinion on the validity of this method. Defense of the method used is beyond the scope of this paper and in the authors' opinion would only prove to be didactic.

Unipolar leads are termed "V" leads. The site of the exploring electrode is designated by a subscript letter from the limb leads. For example, VR—right arm lead, VL—left arm and VF—left leg. Because of the increased voltage when the Goldberger technic is used, the leads are termed "augmented" and are thereby designated as aVL, aVR, and aVF. Precordial or chest leads are designated by number for positions recommended by the American Heart Association (see Fig. 3).

Rosenburg and Agress[7] have demonstrated that the precordial lead sites were well chosen since V_1 and $_2$ and V_5 and $_6$ face the right and left ventricles, respectively, even in presence of hypertrophy. Although this has not been proved to be so by their method in children, tracing patterns would indicate that for the most part such is true. In some cases

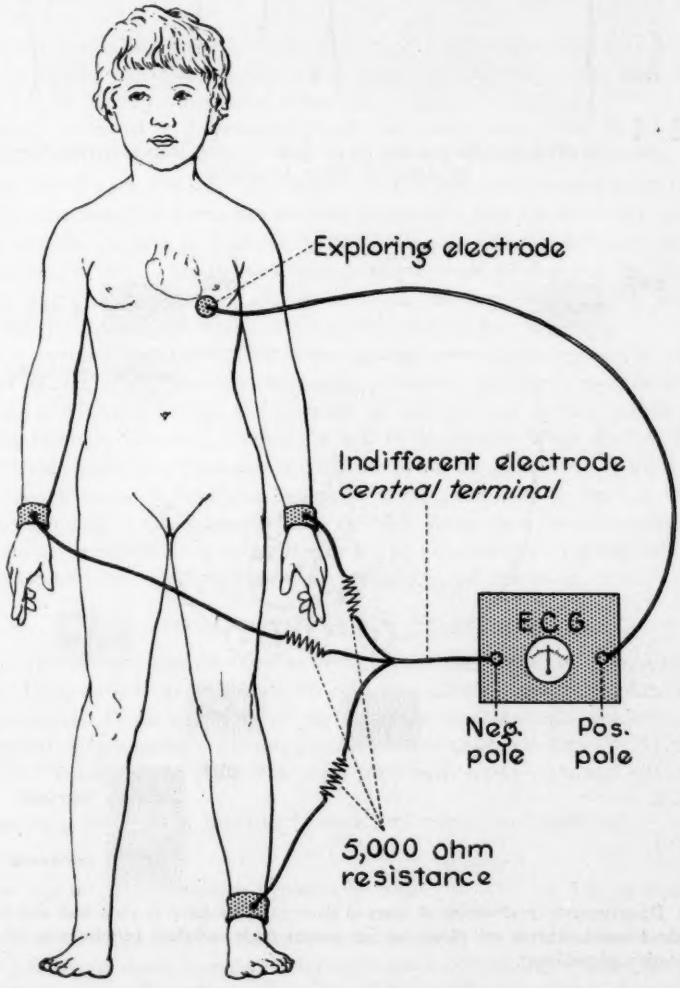


FIG. 2. Drawing showing essential features of unipolar lead electrocardiography as described first by Dr. F. N. Wilson.

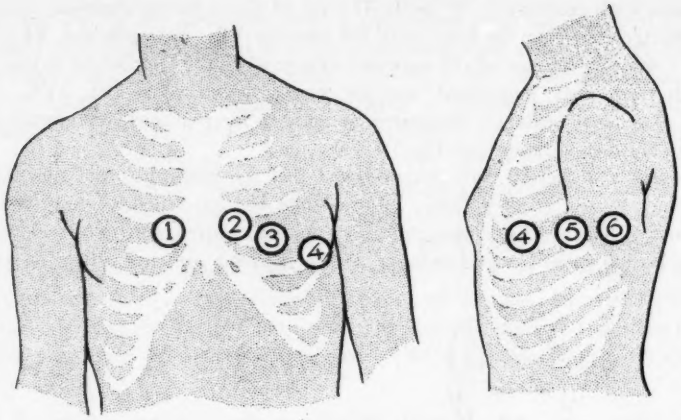


FIG. 3. Drawing showing positions for precordial or chest leads as recommended by American Heart Association.

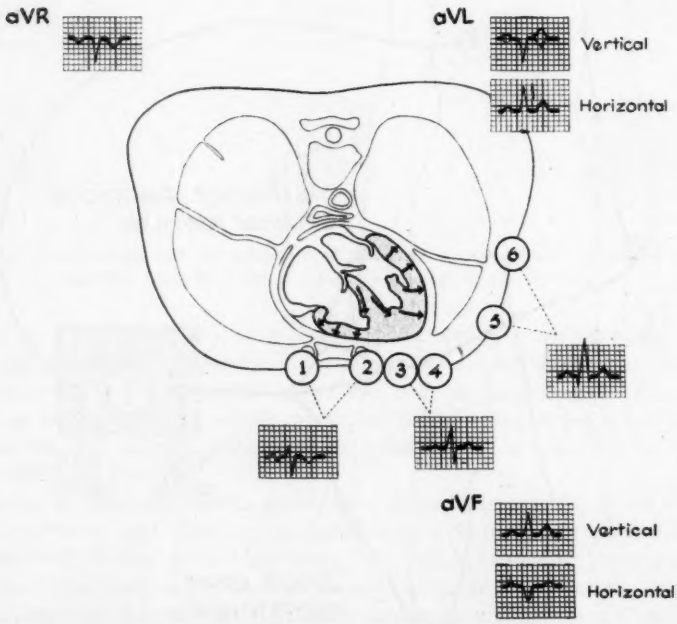


FIG. 4. Diagrammatic cross section of heart to show its relationship to chest wall and position of chest leads. Normal patterns are illustrated for various leads including patterns seen in vertically and horizontally placed heart.

the heart may be rotated on its long axis so that the septum lies more to the left. This is spoken of as clockwise rotation (as though the observer were viewing the heart from below the diaphragm). When this condition is present, left ventricular patterns may not be seen until V_6 or further lateralward. Figure 4 is a diagrammatic cross section of the heart to show its relationship to the chest wall and the position of the chest leads. It will be recalled that the ventricular activation originates in the A-V node and is carried by the bundle of His a short distance along the ventricular septum to the left and right bundle branches. These in turn divide into smaller and smaller branches ending in the so-called Purkinje network which activates the ventricular muscle from the endocardial to the epicardial surface (Fig. 4). The first portion of the ventricular muscle to be stimulated is the septum which is activated from the left to the right by a branch arising from the left bundle branch.

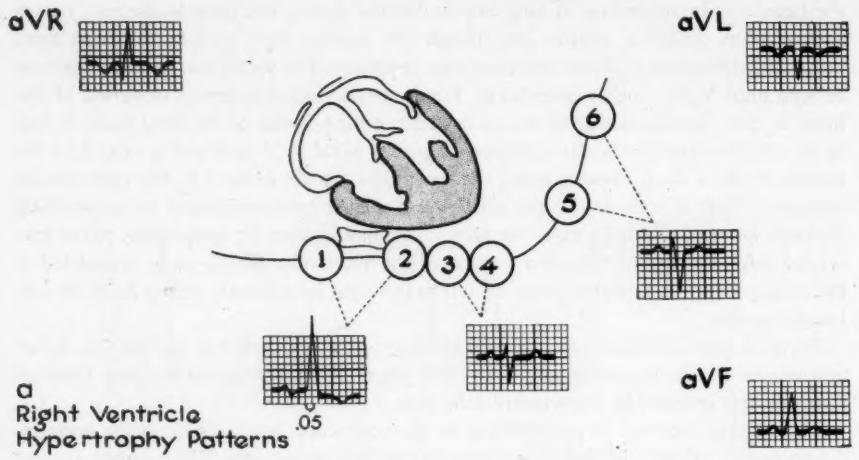
When electric activation moves toward an electrode, it is recorded as positive, i.e., by an upstroke on the electrocardiogram. Conversely when electric activity moves away from an electrode, it is recorded by a downward deflection.

The electric potential is proportional to the ventricular mass. Thus, under ordinary circumstances, the left ventricle exerts more potential than the right. This accounts for the normal pattern of a small R-wave due to ventricular septal activation and a large S-wave due to left ventricular predominance in those leads which face the epicardial surface of the right ventricle (V_1 and $_2$). Conversely, those leads facing the epicardial surface of the left ventricles (V_5 and $_6$) are recorded most usually as a qR pattern (see Fig. 4). Leads V_3 and $_4$, which lie over the area of the ventricular septum, record tracings which are characteristically diphasic and exhibit an RS pattern (see Fig. 4).

Tracings recorded by the limb leads vary according to the electric position of the heart. When the left leg (aVF) lead records tracings resembling those seen over the epicardial surface of the left ventricle (V_5 and $_6$) while the left arm lead (aVL) records tracings resembling those in V_1 and $_2$, the heart is said to be vertical. When the left leg lead records tracings resembling those seen over the surface of the right ventricle while the left arm lead records tracings resembling those over the left ventricle, the heart is said to be horizontal (see Fig. 4). Since the right arm electrode always faces the endocardial surface whether the left ventricle faces the left leg or left arm electric activity always moves away from this electrode and all complexes are therefore directed downward.

Criteria for Ventricular Hypertrophy

When hypertrophy occurs the increase in ventricular mass causes an increase in electric potential. Thus, those leads which face the epicardial surface of a hypertrophied ventricle record an increase in the amplitude of the R-wave while those leads which do not face the epicardial surface record a downstroke of increased amplitude (see Fig. 5). Sokolow and Lyon[1, 2] found that by using R/S ratios from leads facing right and left ventricles a more accurate definition of hypertrophy could be brought into profile, i.e., $\frac{\text{R/S in } V_5}{\text{R/S in } V_1}$ $= 0.4$ or less in right ventricular hypertrophy while $\frac{\text{R/S } V_5}{\text{R/S } V_1} = 100$ or more in left ventricular hypertrophy. When ventricular mass increases, the time for its complete activation is likewise increased, causing a delay in the onset of the intrinsic deflection (see Fig. 5). This is likewise spoken of as prolongation of the ventricular activation time or V.A.T.



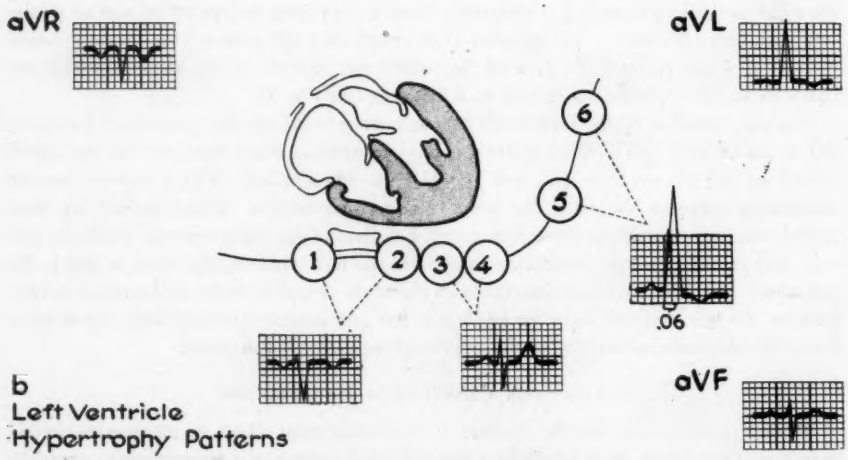


FIG. 5. a. Diagrammatic cross section of heart with right ventricular hypertrophy showing typical patterns found in various leads. Note prolongation of ventricular activation time in V_1 and $_2$. Dotted lines represent normal V.A.T. b. Drawing showing heart with left ventricular hypertrophy and patterns obtained in various leads. Note prolonged V.A.T. in V_5 and $_6$.

If right ventricular hypertrophy is sufficiently marked, a large portion of its epicardial surface may face the right arm electrode which may then record a large R-wave (more than 5 mm.),

RESULTS OF STUDY

Normal Infants and Children

The 50 children used as control groups were from the pediatric wards of University Hospitals, Minneapolis. They were hospitalized for minor or orthopedic surgery and were

TABLE 1

RANGE OF VALUES FROM 50 NORMAL INFANTS AND CHILDREN OF VARIOUS AGES

	Age Group				
	0–½ yr.	½–2 yr.	2–6 yr.	6–10 yr.	10–16 yr.
Axis Devia'n	+60 to +130°	+10 to +78	+52 to +80	−2 to +90	−20 to +92
Elect. Posit'n	1-I; 5-V; 4-S.V.	2-I; 1-S.V.; 4-V.	5-S.V.; 4-V.	3-I; 2-S.V.; 8-V	1-H; 1-S.H. 2-I; 8-V.
R aVR	0 to 5	1 to 5	0 to 5	0 to 3	0 to 3
R V_1	5 to 40	4 to 18	4 to 11	2 to 12	1 to 11
S V_1	15 to 35	1.0 to 9	3 to 14	6 to 22	7 to 18
R/S V_1	.52 to 5.3	1.0 to 10	0.5 to 3.3	0.2 to 0.9	0.1 to 1.2
R V_5	4 to 25	7 to 32	10 to 18	16 to 32	8 to 35
S V_5	2 to 18	3 to 13	1 to 18	3 to 24	1 to 9
R/S V_5	.7 to 10	1.1 to 4	1 to 10	0.8 to 5.5	1.3 to 13
$\frac{R/S\ V_5}{R/S\ V_1}$	.3 to 5.5	.4 to 2.8	0.5 to 6.1	2 to 17.4	1.8 to 110
VAT* V_1	.02 or less	.01 to .03	.01 to .03	.01 to .02	.01 to .03
VAT* V_5	.02 or less	.02 to .03	.02 to .03	.02 to .03	.02 to .04
ST V_1	−1.0 to +1.0	0 to −1.5	0 to +1	−0.5 to +1.0	0 to 1.0
ST V_5	−1.0 to +1.0	0	0 to +1	−0.5 to +1.0	0 to 0.5
T V_1	+1.5 to −5	1.0 to 7	−1 to −4	−1 to −8	+1.0 to −4
T V_5	1.5 to 7	1.5 to 7	2 to 5	1 to 9	2 to 7

* Ventricular Activation Time
V —Vertical
SH—Semi-horizontal
I —Intermediate
SV—Semi-vertical
H —Horizontal

considered to be free of any cardiovascular disease. A summary of the range of values obtained in the various age groups can be seen in table 1.

Axis Deviation: Except for age group, 0 to 6 months where 70% of cases showed +90° or more deviation, right axis deviation was not encountered. The big variation in axis deviation occurred between the first group, 0 to 6 months and 6 months to 2 years, with there being essentially no difference between age groups above that age.

Electric Position: Eighty-six per cent of the cases were either vertical or semivertical in position, which is in keeping with previous reports by Yu, Joos and Katsampes[8] and Switzer and Basoain.[9] Ten per cent of the cases were intermediate in position. Only one case (2%) was semihorizontal and one case (2%) horizontal. Both of these cases were in the 10 to 16 year age group.

Height of R-Wave aVR: In no case did the R-wave exceed 5.0 mm., although this was seen as the maximum height in one case of each of the three younger age groups below 6 years of age. In the two older groups the maximum height seen was 3.0 mm. This finding is slightly different from report of Yu, Joos and Katsampes in that they found maximum voltage of R aVR to be lower in younger age groups and higher in older age groups.

Lead V_1: In children below 2 years of age the R-wave usually exceeded the S-wave in voltage. Generally speaking higher voltages of both the R- and the S-wave were seen in

TABLE 2

RANGE OF VALUES OBTAINED IN PATIENTS WITH VARIOUS CONGENITAL HEART CONDITIONS

	Atrial Defect	Ventricular Defect	Patent Ductus	Coarcta-tion	Tetralogy of Fallot	Isolated Pulmonary Stenosis	P.S. with Atrial Defect	Eisenmenger	A-P Defect	Anomalous Vein
Axis Devia'n	−130 to +180	−155 to +155	28 to 92	12 & 68	−130 to +180	60 to 125	−110 to +148	55 to 178	70 to 85	90 & 130
Elect. Posit'n.	5-V; 2-S.V; 3-S.H.	2-H; 4-I; 1-S.V; 2-V.	4-I; 1-S.V; 12-V	1-H; 1-V	6-V; 3-H; 4-I	5-V; 1-S.V;	3-I; 1-SH; 2-V	1-I; 3-V	2-V; 1-S.H.	1 & V
R aVR	3 to 17	0 to 20	0 to 8	0 & 3	0 to 25	0 to 25	0 to 12	1 to 19	1 to 11	6.5 & 7.0
R V_1	2 to 30	4 to 40	2 to 18	5 & 8	12 to 40	4 to 40	5 to 35	11 to 28	13 to 28	9 & 15
S V_1	0 to 24	1 to 20	4 to 40	30 & 32	0 to 6	0 to 12	0 to 25	0 to 20	1 to 30	0 & 3
R/S V_1	.4 to 14.7	0 to 32	.2 to .9	.17 & .25	1 to 40	.3 to 40	.3 to 8	1 to 18	.9 to 13	3 & >15
R V_6	10 to 30	14 to 35	.15 to 40	30 & 32	1 to 27	10 to 40	1 to 22	15 to 24	15 to 26	9 & 13
S V_6	7 to 40	0 to 25	1 to 18	2 & 3	5 to 35	2.5 to 20	3 to 30	8 to 30	10 to 25	10 & 28
R/S V_6	.08 to 2.3	.9 to 20	1.2 to 8.5	10 & 16	.09 to 2.2	.9 to 13	.09 to 5	.5 to 3	.8 to 2.6	.5 to .9
R/S V_6 / R/S V_1	.01 to 5.8	.05 to 85	3 to 35.6	59 & 64	.01 to .73	.05 to 13.3	.03 to .83	.06 to 3	.2 to 1.1	.06 to .16
VAT* V_1	.02 to .06	.02 to .04	.01 to .03	.02	.02 to .06	.02 to .06	.02 to .05	.02 to .06	.03 to .06	.04 & .06
VAT* V_6	.02 to .03	.03	.02 to .05	.04	.02 to .04	.02 to .05	.01 to .03	.02 to .04	.02 to .06	.02
ST V_1	−1 to +1	0 to −1.0	0 to 1	.5 & 1.0	−1.0 to +.5	−2 to +1	−2.5 to +2	−1.0 to +0.5	−.5 to +1.5	−.7 & +1.0
ST V_6	0 to +1	−1.5 to +1.0	−1 to +1	0	−1.0 to +1.0	−3.5 to +1	0 to 1	−1.0 to +2.0	0 to .5	0 & 2.0
T V_1	−5 to +1.5	−5 to +3	−5 to +3	−6 & +2	−5 to +3	−7 to +2	−7 to +5	−.5 to +4	−2 to +4	−7 & +2
T V_6	1 to 5	−7 to +7	−1 to +16	2 & 6	−2 to +6	−12 to +8	3 to 10	1 to 3	−2 to +5	−1.0 & +4

* Ventricular Activation Time: V—Vertical, SV—Semi-Vertical, H—Horizontal, SH—Semi-Horizontal, I—Intermediate.

infants below 6 months of age. There was no essential difference between R/S ratios in the two younger age groups between 0 to 6 months and 6 months to 2 years. Above the age of 6 years the R-wave exceeded the S-wave in voltage in only one case so that for this one exception the R/S ratio varied from 0.1 to 0.9. The ventricular activation time never exceeded .03 seconds. In the age group 0 to 6 months the ventricular activation time was never more than .02 seconds. The ST segment except for three cases in 0 to 6 months group was either isoelectric or elevated up to 1.0 mm. In 2 of those 3 cases the ST segment was depressed a 0.5 mm. while the third was depressed a full mm.

In only six cases was the T-wave positive and in none of these did the deflection exceed 1.5 mm. Four of the six cases were in the 10 to 16 year age group while the other two were in the two youngest age groups. In only two cases did the negative deflection exceed 5 mm. Since inversion of the T-wave is a normal finding in infants and children, its inversion cannot be used as supportive criteria for right ventricular hypertrophy as proposed by some[2] whose figures are largely from adults.

Lead V_5—In only three cases did the S-wave exceed the R-wave in voltage. Two of the three cases were found in the younger age group (2 and 3½ months). The third case was encountered in the 6 to 10 year old group with the R/S ratio being 0.75. There was only a slightly higher average mean and higher maximum R/S ratio as the age scale was ascended, e.g., 0.7 to 10.0 with average of 2.33 in 0 to 6 months and 1.3 to 13 with average of 5.56 in 10 to 16 year age group. The ventricular activation time never exceeded .03 seconds in any age group. The ST segment was never elevated more than 1.0 mm. or depressed more than a 0.5 mm. in any age group. The T-wave was always positive and varied in voltage from 1.0 to 9 mm. with no appreciable difference in range or mean values between any of the age groups.

R/S V_5 : R/S V_1 Ratio: This ratio showed a gradual but step-like increase in both mean and range values concomitant with age groups. There was only one case with ratio below 0.4. This was 0.26 and was encountered as might be expected in the first age group. The lowest figure obtained in the two oldest age groups was 1.8. The highest figures obtained in the lower age groups below 6 years was 6.1. The upper limits was considerably extended in the older age groups. A ratio of 110 was present in one case in the 10 to 16 year old group; the next highest was 26 in this age group and 17.4 in the 6 to 10 year old group. These computed ratios compare favorably with those computed from figures borrowed from other investigations.[8, 10]

Children With Congenital Heart Disease

A summary of the range of values obtained in patients with the various congenital heart conditions can be seen in table 2.

1. Interatrial Septal Defect:

Of the 10 cases of interatrial septal defects, seven were thought to have tracings typical of right ventricular hypertrophy exhibiting an R-wave exceeding 5 mm. in amplitude in aVR, R-wave predominance in V_1 and S-wave predominance in V_5 with an R/S V_5 : R/S V_1 ratio of .73 to .01, and a V.A.T. of .04 or more in V_1 ST segment and T-waves exhibited no characteristic or consistent findings and it was found that the R/S ratios were of more value than were ST and T-wave changes in predicting ventricular predominance.

The unipolar lead tracings in five cases offered information which either changed the interpretation given by the standard leads or offered a sufficient amount of supplemental

information that a definite diagnosis could be established. In Patient P.A. the standard leads were interpreted as being abnormal because of a first degree heart block and large diphasic QRS complexes compatible with congenital heart disease[11] but no definite ventricular predominance was demonstrated (axis deviation $+30°$). However, unipolar limb and precordial leads clearly demonstrated the presence of right ventricular hypertrophy. Large diphasic QRS complexes were encountered in L.J.'s standard lead tracing which gave an axis deviation of a minus 130°, suggesting left ventricular hypertrophy. Precordial leads, however, were typical of right ventricular hypertrophy. The standard lead tracings on L.R. were within normal limits, but right ventricular hypertrophy was clearly demonstrated by precordial lead tracings. The QRS complexes were all predominantly downward in standard leads in another case (R.S.) giving rise to axis deviation of $-50°$. Unipolar limb and precordial leads showed right ventricular hypertrophy. Because of diphasic QRS complexes the standard lead tracings on J.Z. were interpreted as being abnormal and compatible with congenital heart disease.[11] Right ventricular hypertrophy was not proved conclusively until precordial leads were taken.

2. Interventricular Septal Defects:

In the nine cases of interventricular septal defect, the value of the unipolar lead was clearly demonstrated. In 5 of the 9 cases, unipolar tracings either differed in the interpretation from the standard leads or added sufficient information that a more accurate electrocardiographic diagnosis could be made. The standard lead tracings from (S.C.) showed definite left axis deviation ($-45°$). The axis deviation was shown by the limb leads to be positional and no ventricular predominance could be demonstrated. The standard lead tracings in J.E. and P.S. were considered to be abnormal because of large diphasic QRS complexes. The precordial leads showed the presence of right ventricular hypertrophy as discussed below. In two cases (N.T.) and (R.W.) the standard lead tracings were considered to be abnormal because of a left axis deviation ($-52°$ and $-30°$) but unipolar limb and precordial leads failed to demonstrate left ventricular predominance. In case of R.W. it was thought that there was strong evidence for both right and left ventricular hypertrophy from the precordial leads. The reason for suspecting right ventricular hypertrophy was an R/S V_1 ratio of 6 and a prolonged V.A.T. in V_1 of .04. The R/S ratio in V_5 was 20 and the T-wave was only 2 mm. in height giving an R/T ratio of 10, strongly suggesting left ventricular hypertrophy.[1] The R/S V_5 : R/S V_1 ratio was within normal limits.

Three cases were thought to show patterns of definite right ventricular hypertrophy. In these three cases there was apparently a sufficiently large shunt that a mild degree of right ventricular hypertension was present (40 to 45 mm.Hg). There was likewise radiographic evidence of mild right ventricular hypertrophy. These tracings (J.E., P.S. and M.S.) exhibited classical patterns of high R-waves in V_1 and large S-waves in V_5 so that R/S ratios fitted previous defined criteria for right ventricular hypertrophy. The R/S ratio in V_1 varied between 5 and 32, while in V_5 it varied from 1.8 to 0.9. The R/S V_5 : R/S V_1 ratios in these three cases were well below normal range and varied from 0.05 to 0.18. The R-wave in aVR varied from 8 to 20 which was well above the normal maximum of five encountered in this series of normal controls. The ventricular activation time in all three cases was prolonged (.04 to .05) above the normal limit of .03 in the control series.

The ST segment offered no consistent finding since in one case (J.E.) it was depressed in leads V_1 and V_5, while in another (N.S.) it was depressed in V_1 and elevated in lead V_5, and in the third case (P.S.) it was isoelectric in V_1 and elevated 0.5 mm. in lead V_5.

In all other cases it was isoelectric. The T-waves likewise offered no specific pattern but were unusual in that in 2 of the 3 cases T V_1 was diphasic while in the third the T-wave was positive to a 3 mm. height. One case (J.E.) showed a T-wave of −7 mm. in V_5, otherwise the T-waves in this lead were within normal limits.

3. Patent Ductus Arteriosus:

Unipolar lead tracings in the 17 cases of patent ductus arteriosus studied changed the interpretation of standard lead tracings in only four of the cases. The lower percentage of change in diagnosis in this group as compared with interatrial and interventricular septal defects is in all probability due to the fact that the standard leads appeared normal in all but one case (M.C.). Although the R/S V_5 : R/S V_1 ratio had much higher mean and range as compared with interatrial septal defect and interventricular septal defect, they were all within normal limits, except for the four cases below.

Case M.B. limb leads showed a vertical heart with clockwise rotation so that in the standard leads a slight right axis deviation was obtained (+92°). The degree of clockwise rotation was so marked that a left ventricular pattern was not seen until V_6 position was taken. The V_5 tracing differed little from V_3 and V_4 and it was obvious that this tracing was taken in an area overlying the ventricular septum. Because of the clockwise rotation the values from V_6 were substituted for V_5 changing the R/S V_5 : R/S V_1 ratio from 4.8 to 33.3. Three other cases (E.H., G.J. and M.D.), although not showing definite hypertrophy by usual standards, i.e., depressed ST and lower inverted T-waves, did show as did M.B. left ventricular predominance as evaluated from R/S ratios (18 to 36) in comparison with normal values for their age groups.

4. Coarctation of the Aorta:

Two cases of coarctation of the aorta were studied. In both of these cases the standard leads were within normal limits. However, precordial lead tracings revealed an R/S V_5 : R/S V_1 ratio of 58.8 in one and 64 in the other. Neither case displayed any ST segment displacement of T-wave changes suggestive of a strain pattern in either the standard or unipolar chest or limb leads.

5. Tetralogy of Fallot:

Thirteen cases of tetralogy of Fallot were analyzed. Two cases exhibited downward QRS complexes in all three standard leads without ST or T-wave changes. Unipolar limb and precordial lead tracings established the presence of right ventricular hypertrophy. Both the standard leads and unipolar leads were compatible with right ventricular hypertrophy in the remaining cases with one exception (S.P.). S.P. showed an axis deviation of +85° and standard leads were interpreted as being within normal limits. Unipolar leads while not fulfilling complete criteria for right ventricular hypertrophy, indicated right rather than left ventricular predominance. (R/S V_5 : R/S V_1 = .73.)

6. Isolated Valvular Pulmonary Stenosis:

When the data from the six cases of isolated valvular pulmonary stenosis had been compiled, the results appeared to be disappointing since only two cases (L.R. and T.R.) had "classic" criteria for right ventricular hypertrophy. Three cases (J.R., C.F. and G.E.) had tracings which were well within normal limits. The diagnosis of pulmonary stenosis in all six patients was based in part upon the findings obtained by heart catheterization. In general, the correlation between the right ventricular pressures so obtained and the electrocardiographic findings was not as good as was anticipated; i.e., some patients had marked

right ventricular hypertension (pressure 120 mm. mercury) with minimal electrocardiographic changes. The remaining case, S.K., had a marked degree of pulmonary stenosis. The right ventricular pressure on catheterization was found to be 250 mm.Hg. In addition there was radiologic evidence of marked right ventricular hypertrophy. Over the entire precordium (V_1 to V_6), precordial leads showed essentially the same pattern of a small Q and a large R-wave with depressed ST segment and inverted T-waves. It would seem safe to assume from the above that in this patient all leads were facing the epicardial surface of the markedly hypertrophic right ventricle which exhibited clockwise rotation.

7. Pulmonary Stenosis with Interatrial Communication:

Six cases of pulmonary stenosis with interatrial communication were studied. In three cases the unipolar leads lead to a different interpretation than standard lead diagnosis. Two of the cases (D.C. and J.L.) had slight right axis deviation on standard leads but no definite right ventricular hypertrophy was evident until unipolar lead tracings were taken. Case G.A. exhibited downward QRS complexes in all standard leads and an axis deviation of a $-110°$. Unipolar lead tracings revealed a definite right ventricular hypertrophy pattern. Two cases (J.G. and R.W.) exhibited what has been described as atypical right ventricular hypertrophy patterns.[4] The QRS complexes in these cases showed a much deepened S-wave which was present over both sides of precordium. The R/S V_5 : R/S V_1 ratio, however, still was computed to indicate right ventricular predominance.

8. Eisenmenger's Complex:

Four cases of Eisenmenger's complex were studied. Two of the four cases (A.W. and B.R.) had tracings typical of right ventricular hypertrophy in both the standard and unipolar leads. In addition, B.R. showed low voltage in TV_5. Case V.D. showed diphasic QRS complexes with low voltage of the T-wave in lead 1 in the standard leads. In the unipoplar leads the R-wave in aVR was 19 mm., while in the precordial leads the QRS complexes showed a tendency to high voltage and to be diphasic; the V.A.T. was prolonged over both ventricles and the T-wave in V_5 exhibited low voltage. Although the R/S V_5 : R/S V_1 ratio indicated mild right ventricular predominance, it was thought that the high voltage diphasic QRS complexes and low voltage T V_5 was indicative of combined ventricular hypertrophy. The fourth case, C.H., displayed an abnormal standard lead tracing suggesting left ventricular strain. The unipolar leads showed a high R and inverted T in aVL and a slightly depressed ST segment with a low voltage T-wave in V_6. The precordial QRS complexes were diphasic over both sides and R/S V_5 : R/S V_1 ratio was 3.0. It was thought that this tracing likewise was compatible with combined ventricular hypertrophy.

9. Aortic-Pulmonary Septal Defect:

Three cases of aortic-pulmonary septal defect were studied. Case J.A. standard leads showed a deep S_1 and depressed ST segments and diphasic T-waves in leads 2 and 3. The limb leads showed a semihorizontal heart. The R-wave in aVR was 11.0 mm. in height. The R-wave in aVF was 40 mm. in height and the ST segment was depressed and the T-wave was diphasic. The precordial leads showed high voltage diphasic QRS complexes of RS pattern type over both ventricles. The R/S ratios were within normal limits but because of the high voltage of the diphasic QRS complexes across the precordium it was thought that such a tracing showed evidence of hypertrophy of both ventricles. This would seem to fit well with the clinical picture since the right ventricular pressure in this case was found to be 65 mm.Hg.

The standard leads in J.H. were interpreted as being abnormal and exhibited left ventricular strain. The limb leads showed a vertically placed heart and were not unusual except for ST segments which were elevated in aVR and depressed in aVF. The precordial leads showed high voltage diphasic QRS complexes of RS pattern across entire chest as was present in tracings taken on J.A. The R/S V_5 : R/S V_1 ratio was 0.9. The T-wave was diphasic in V_5, but there was no ST displacement. This tracing was likewise interpreted as exhibiting both right and left ventricular hypertrophy. The right ventricular pressure in this case was 40/20 mm. mercury.

The third case K.N. showed a striking similarity in the standard leads to J.H. in that T-wave in lead one was isoelectric and QRS 2 and 3 had high voltage with deep S-waves. The heart was vertically placed and R-wave in aVR was 6 mm. in height. There were no significant ST or T-wave abnormalities in the limb leads. The QRS complexes in the precordial leads were suggestive of right ventricular hypertrophy with R/S V_5 : R/S V_1 ratio 0.20. The T-wave in V_5, however, was inverted and this tracing as well as the other two with this anomaly was thought to suggest combined ventricular hypertrophy.

10. Anomalous Pulmonary Vein Emptying Into the Right Atrium:

Two cases of anomalous pulmonary vein which emptied into the right atrium were studied. In one case the standard leads showed marked right axis deviation and were interpreted as exhibiting right ventricular hypertrophy. The unipolar limb and precordial leads gave complete confirmation by standards previously described. In the other case the standard lead tracing was interpreted as abnormal but no definite ventricular predominance or hypertrophy was demonstrated. However, limb and precordial leads gave definite evidence of right ventricular hypertrophy.

Discussion

From the experience of this series of cases we concur in the conclusion of others[3, 4, 12] that unipolar lead electrocardiography is so much more reliably informative than standard limb lead electrocardiography that no case of congenital heart disease should be considered adequately studied without its use. It was interesting to note that in this series the unipolar leads appeared to be of the most value in those cases (interventricular septal defect, anomalous pulmonary vein, interatrial septal defect and patent ductus arteriosus) where demonstration of hypertrophy by "conventional" methods frequently is the most difficult.

Computation of R/S ratios and particularly R/S V_5 : R/S V_1 ratio proved to be by far the most reliable indication of ventricular hypertrophy. Contrary to the findings of other investigators whose work has largely been with adults, ST segment and T-wave changes in this series were not found with sufficient frequency to be considered as reliable evidence of ventricular hypertrophy except as associated with R/S ratios. Next to the R/S ratios the most consistent finding was a prolongation of the V.A.T. beyond .03 seconds in either V_1 or V_6. In cases of right ventricular hypertrophy an R-wave in aVR exceeding the maximum normal height of 5 mm. was encountered in nearly every case.

From the data compiled for the R/S V_5 : R/S V_1 ratio, it would appear that the normals for each group will fall within the range given below:

1-6 mo.	0.2 to 6
½-2 yr.	0.4 to 8
2-6 yr.	0.5 to 10
6-10 yr.	1.0 to 20
10-16 yr.	1.5 to 45

In all cases in which right ventricular hypertrophy was considered to be present, the above ratio was always below the minimum figure quoted above for each age group. The number of cases of left ventricular hypertrophy in this series was small and warrants further study. However, in all cases in which left ventricular hypertrophy was considered to be present, the above ratio was above the normal limit figures given above.

Several cases in which both the right and left ventricle were thought to be hypertrophied were found to have high voltage diphasic QRS complexes over the entire precordium. It was in these cases that changes in T V_5 (low voltage in presence of a high R-wave) aided in the diagnosis of left ventricular hypertrophy.

The reader is cautioned always to identify both ventricular patterns before computing R/S ratios, since clockwise rotation of the heart may cause left ventricular pattern to be hidden until V_6 (or further lateralward).

Summary

A brief discussion of theory of unipolar lead electrocardiography has been presented. The findings on 50 normal infants and children and 72 cases of congenital heart disease have been presented. The advantage of the unipolar limb and precordial leads over standard electrocardiography has been confirmed by the study presented. The R/S ratios and ventricular activation time offered more reliable criteria for hypertrophy than did the ST segment and T-wave changes.

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Spanish Abstract

Derivaciones Unipolares Electrocardiograficas en Niños, con Referencia Especial a su Valor en las Cardiopatias Congénitas

Según los autores los trazos electrocardiográficos tomados en las derivaciones "standard" a menudo no proporcionan toda la información deseada. Se emprendió este trabajo con el objeto de establecer un criterio electrocardiográfico bien definido, para determinar la hipertrofia ventricular,

usando las derivaciones unipolares. Se estudiaron 72 enfermos con cardiopatías congénitas comprobadas por cateterización cardiaca, intervención quirúrgica o estudio post-mortem, comparándolos con una serie de 50 niños con corazones normales, los que se dividieron en 5 grupos de acuerdo con la edad. Se estudiaron los trazos obtenidos en ellos, y compararon con los encontrados en los pacientes con cardiopatías congénitas. En este último grupo hubo 10 con defectos del tabique interauricular; 9 con anomalías del tabique interventricular; 17 con persistencia del conducto arterioso; 2 con coartación de aorta; 13 casos de tetralogía de Fallot; 3 casos de estenosis de la pulmonar aislada; 6 enfermos con estenosis de la pulmonar asociada a comunicación interauricular; 4 con complejo Eisenmenger; 3 con defectos del tabique aórtico pulmonar y finalmente 2 casos con desembocadura de vena pulmonar anómala en auricula derecha.

Por la experiencia derivada del presente estudio se puede concluir que la electrocardiografía unipolar proporciona, en las cardiopatias congénitas, mayor información que las derivaciones "standard," siendo de valor sobre todo cuando los métodos convencionales presentan serias dificultades para la demostración de la hipertrofia ventricular. Para demostrar la hipertrofia ventricular el dato de mayor valor fué el cómputo de la relación R/S, siguiéndole en importancia al respecto la prolongación del tiempo de aparición de la deflección intrínseca por más de .03 segundos en V_1 ó V_6. En la hipertrofia ventricular derecha se encontró casi siempre una onda R en aVR que excedía la altura normal máxima de 5 mm. El número de enfermos con hipertrofia ventricular izquierda aquí analizados es demasiado pequeño y se requieren mayores estudios. Varios pacientes con hipertrofia ventricular tanto derecha como izquierda tuvieron complejos QRS difásicos de alto voltaje sobre toda la región precordial. Fué en ellos en los que los cambios en TV_6 (voltaje pequeño en presencia de una onda R alta) ayudaron para el diagnóstico de la hipertrofia ventricular izquierda.

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Q-T INTERVAL DURING ACTIVE AND INACTIVE RHEUMATIC FEVER

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DURING the past few years several reports have appeared with various findings and conclusions concerning the significance of the Q-T interval of the electrocardiogram in rheumatic fever. It has been postulated by some authors that abnormal lengthening of the Q-T interval may be used as an index of the presence of active rheumatic myocarditis. It is generally accepted that the beginning of the inscription of the Q-wave of the ECG represents the beginning of depolarization of the ventricular muscle in electrical systole, and that the end of the T-wave marks the completion of repolarization.

The length of the Q-T interval is known to be dependent on the heart rate, being longer at slow rates and shorter at fast rates. To relate the Q-T interval and rate several formulae have been proposed.[1-5] Bazett's formula,[1] where $K = \frac{Q\text{-}T}{\sqrt{R\text{-}R}}$, R-R being the measure of cycle length in seconds, was used in this material. The constant of Bazett's formula is expressed as the corrected Q-T (abbreviated as Q-Tc), as suggested by Taran and Szilagyi.[6] Normal values in infants and children have been reported by various authors.[7-10]

There are various factors which affect the duration of electrical systole. The Q-T interval is prolonged in hypocalcemia and hypopotassemia[11] and shortened in hypercalcemia.[12] Quinidine prolongs the Q-T interval[13] while digitalis shortens it.[14] The Q-T interval was found to have been prolonged in a significant number of cases in which nonrheumatic myocarditis was established by necropsy findings.[15] Prolongation has also been reported in patients with recent myocardial infarction.[16] Shortening of the Q-T interval is reported in the presence of pericarditis with effusion both of tuberculous[17] and rheumatic[18] etiology. In the presence of ventricular hypertrophy and in congestive failure, the Q-T interval may be prolonged.[19, 20]

Findings and opinions expressed in the recent literature differ concerning the behavior of the Q-T interval during the active and inactive phases of the rheumatic process. Taran and Szilagyi[6] consider the Q-Tc an index of activity in that they found prolongation of the Q-Tc interval in all their patients with acute rheumatic carditis, while it was normal in all their patients during the inactive phase. Abrahams[21] reported prolongation of the Q-Tc interval in almost all his patients with active carditis. However, he noted prolongation also in some of his patients with inactive rheumatic heart disease, and in some rheumatic subjects who demonstrated neither rheumatic activity nor organic heart disease at the time of observation. Pokress and Goldberger[22] found a lower incidence of prolongation during rheumatic activity than that reported by Taran and Szilagyi.

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Epstein and Gardam[23] noted a prolongation of the interval in 38% of ECGs taken during active carditis and in 27% of the tracings in these same patients during the inactive phase, and concluded that a prolongation of the Q-Tc interval per se is not diagnostic of active rheumatic carditis.

Craige et al.,[24] using their average normal value plus two standard deviations[8] as the upper limit of normal, found that the Q-Tc interval did not exceed this value in any of their patients with acute rheumatic fever, including those who had fatal pancarditis. In these two groups, however, the average Q-Tc interval was slightly longer than that of their normal control subjects. It was further observed by these authors that the Q-Tc intervals in quiescent rheumatic heart disease were similar to the values found in the series of normal children. They concluded on the basis of the infrequency of definite Q-Tc abnormality in their series that this measurement is of limited usefulness as an estimate of activity.

Clinical Material and Methods

The purposes of this study were to review the behavior of the Q-T interval during the active phase as well as during the period of inactivity of the rheumatic process. A review and comparison of concomitant incidence of prolongation of the P-R interval was included. In addition analysis was made of the incidence of heart disease as related to the course of the Q-T interval in patients observed for considerable periods of time after subsidence of the rheumatic activity.

A review was made of the records of all cases admitted to the Bellevue Hospital Children's Medical Service with active rheumatic fever and chorea during the years 1940-1947 inclusive. Cases with congestive failure, receiving digitalis, or those whose records contained inadequate electrocardiographic data were excluded from this study. The ECGs and clinical records of 249 episodes of active rheumatic fever and chorea occurring in 208 patients (102 boys and 106 girls, ranging in age from 3 to 13 yr.) were analyzed. Analysis was made of the records of those 119 patients from the above hospital group who were subsequently under the observation of the Children's and Adolescents' Cardiac Clinics. Clinic visits varied in interval from 1 to 6 mo., during periods of follow-up observation of from 1 to 9 yr.

ECGs of 79 normal children of similar age were reviewed to obtain our normal values for the Q-Tc. A string galvanometer instrument, either Cambridge or Sanborn, had been used in recording all ECGs. The Q-T interval was measured in Lead II of the ECG from the beginning of the Q-wave as determined by the slightest initial deflection from the isoelectric line to the end of the slope of the downstroke of the T-wave. The measurements were made with calipers under a magnifying glass. The average Q-T interval and cycle length were calculated from a total of 6 to 12 measured complexes. The P-R interval was also determined at the same time as the Q-T measurements were made. The P-R interval was measured from the beginning of the upstroke of the P-wave to the initial deflection from the base line of the QRS complex. The longest P-R interval observed in Leads I, II or III, usually Lead II, was recorded. The observed P-R intervals were compared with the normal values for this measurement for age and rate as given in tables by Ashman and Hull.[4] All readings were made by one observer (S. F.).

ECGs were rejected if they were technically imperfect due to wandering base lines, alternating current interference, or improper standardization. The presence of an isoelectric Q-wave or T-wave or fusion of the T-wave with the following P-wave causing uncertainty as to the exact beginning of the Q-wave or the end of the T-wave were additional reasons for rejecting ECGs.

Study of Q-Tc and P-R Interval in Normal Subjects: Seventy-nine ECGs obtained in 49 normal boys and 30 normal girls ranging in age from 2 to 12 yr. were analyzed. These were children in the Pediatric Clinic who had no evidence of rheumatic fever or heart disease. The average Q-Tc obtained in this group was 0.418 with a standard deviation of 0.016. Figure 1 shows the distribution of Q-T intervals at corresponding cycle lengths.

The value set for the upper limit of normal was the average figure +2 standard deviations, as statistically such a value includes 95% of cases in a normal distribution curve. For purposes of comparison with other papers the findings from this material have been analyzed and presented as to the values which exceeded the normal average +1 standard deviation (1 S.D.) and those values which

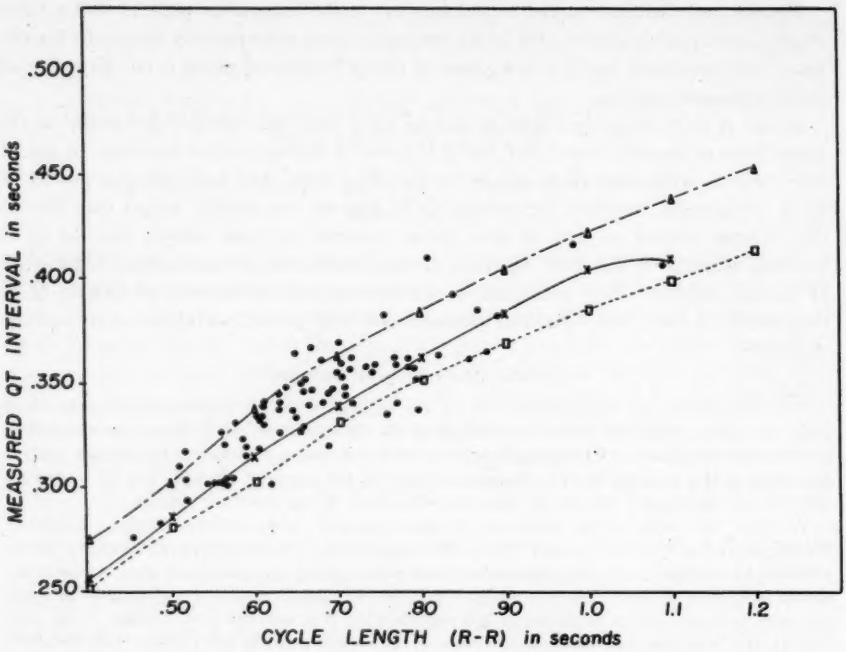

FIG. 1. Distribution of measured Q-T intervals at corresponding cycle lengths in 79 normal children. Curve for Bazett's formula (×) and curves for average normal (□) and upper limit of normal (Δ) values in children and men as given by Ashman and Hull are drawn in for comparison. KEY:

● = present series of 79 normal controls.
× = curve for Bazett's formula (K = .405).
□ = Ashman and Hull's average normal values for children and men.
Δ = Ashman and Hull's upper limit of normal values for children and men.

exceeded the normal average +2 standard deviations (2 S.D.). This was done inasmuch as some authors apparently take the upper limit of normal as the average plus 1 S.D. while others set this value at the average plus 2 S.D.

In our 79 normal subjects the Q-Tc was found to exceed the average normal plus 1 S.D. (0.434) in 10 individuals and in 3 of these 10 the value exceeded the average normal plus 2 S.D. (0.450) as shown in table 1.

In a series of 517 normal infants and children reported by Alimurung et al.,[8] the average Q-Tc value found was 0.404 with a standard deviation of 0.026. Of these 517 normals there were 60 individuals in whom the Q-Tc exceeded their average plus 1 S.D. (0.430) and in 11 of these 60 the value exceeded their average plus 2 S.D. (0.456).

In the ECGs of our 79 normal children the P-R interval was found to be prolonged for age and rate in 4 instances.

RESULTS

The cases with manifestations of the active rheumatic process reviewed in this series are divided into several groups. There were 128 patients in whom physical findings indicated active rheumatic carditis; 13 patients with polyarthritis or chorea in whom the only evidence of active carditis was a prolonged P-R interval; 20 patients with polyarthritis but no clinical evidence of carditis and normal P-R intervals; 47 patients with chorea who had

no other clinical or laboratory evidence of rheumatic activity during hospitalization.

From the above groups of those 97 patients who had had a Q-Tc greater than the average normal plus 1 S.D., the following numbers were among those subsequently observed during the inactive phase in the Cardiac Clinics. There were 73 of the group who had had obvious carditis, 7 of the group with chorea or polyarthritis with prolongation of the P-R interval, 13 of the group who had had only polyarthritis, and 4 of the chorea group. Three of the group with chorea or polyarthritis with prolongation of the P-R interval and 19 of the chorea group had had a Q-Tc value less than the average normal plus 1 S.D. during the acute episode. In these 22 cases the Q-Tc remained below this value during the follow-up period.

TABLE 1

Q-Tc and P-R Interval During Rheumatic Activity

	No. of Cases	No. of Episodes	Q-Tc			P-R	
			Per Cent of Episodes			Per Cent of Episodes	
			Normal Q-Tc	Exceeding Average Normal Q-Tc		Normal P-R interval*	Abnormal P-R interval
				+1 S.D. But <2 S.D.	+2 S.D.		
Active carditis	128	169	8%	22.5%	69%	64%	36%
Prolonged P-R as only evidence of carditis	13	13	31	31	38.5	0	100
Polyarthritis without carditis	20	20	30	20	50	100	0
Chorea without carditis	47	47	66	17	17	100	0
Normals for comparison	79	—	87.3	8.9	3.8	95	5

* According to criteria for age and rate as given by Ashman and Hull.[4]

Q-Tc and P-R Intervals During Active Rheumatic Phase

Table 1 summarizes in percentage form the Q-Tc findings observed in the various groups as outlined above. The figures are divided to show the per cent of observations greater than the average normal plus 1 S.D. but less than 2 S.D., and the per cent of observations greater than the average normal plus 2 S.D.

Review of the records of the 169 episodes of active carditis showed that in one or more electrocardiographic records the Q-Tc value exceeded the average normal plus 1 but less than 2 S.D. in 38 instances (22.5%) and exceeded the average normal plus 2 S.D. in 118 instances (69%). In the remaining 13 episodes, although the Q-Tc was less than the average normal plus 1 S.D., in but three instances was the Q-Tc value less than the average normal figure (0.418). In only one of these 13 patients with Q-Tc within normal limits was there evidence of pericarditis. In the above patients with active carditis the P-R interval was prolonged in at least one ECG during 61 or 36% of the total episodes. Prolonged conduction time was present in only one of those 13 episodes in which the Q-Tc was less than the average normal plus 1 S.D.

Criteria used for the diagnosis of active carditis had included tachycardia out of proportion to the temperature, rapid sleeping pulse rate, gallop rhythm, changing murmurs, appearance of new murmurs, and change in heart size as noted radiographically.

Thirteen patients in whom the only suggestion of active carditis had been prolongation of the P-R interval for age and rate are considered separately from the above group. In these the predominant feature of the rheumatic process was polyarthritis in 10 and chorea in 3 patients. Q-Tc exceeded the average normal plus 1 but less than 2 S.D. in 4 patients (31%) and exceeded the average normal plus 2 S.D. in 5 patients (38.5%). In the remaining 4 patients the Q-Tc was less than the average normal plus 1 S.D., and in 1 of these the value was less than the average normal figure.

A group of 20 patients had rheumatic polyarthritis with no clinical evidence of active carditis nor abnormal P-R interval. In one or more of the electrocardiographic records taken during these episodes the Q-Tc value exceeded the average normal plus 1 but less than 2 S.D. in 4 episodes (20%) and exceeded the average normal plus 2 S.D. in 10 episodes (50%). In 5 episodes the Q-Tc value fell between the average and the average normal plus 1 S.D., and in 1 the Q-Tc was less than the average normal figure (0.418).

There were 47 cases hospitalized for active chorea with no clinical evidence of active carditis nor abnormal P-R intervals, and in whom the erythrocyte sedimentation rate was normal. The Q-Tc was greater than the average normal plus 1 but less than 2 S.D. during 8 episodes (17%) and greater than the average normal plus 2 S.D. during 8 episodes (17%). The Q-Tc was less than the average normal plus 1 S.D. in 31 episodes and in these, 12 were less than the average normal figure.

Q-Tc and P-R Values as Observed in Patients Subsequently Followed in the Cardiac Clinics During the Inactive Phase

Of those patients whose hospital records of active rheumatic episodes were analyzed, 97 of those who had had a Q-Tc higher than average normal plus 1 S.D. were subsequently observed during the inactive phase in the Childen's and Adolescents' Cardiac Clinics for periods of time varying from one to nine years. In all cases the rheumatic process was considered quiescent by the end of hospitalization. For the purposes of this study, in order to obviate the influence of recurrent rheumatic activity, the period of follow-up observation analyzed for each case was that period which followed either a single attack or the last of multiple attacks of recurrent rheumatic activity.

Table 2 summarizes the findings in these 97 patients as to Q-Tc values present during the inactive phase observation periods. These are again grouped as in table 1 according to type of manifestations of rheumatic activity present during the acute phase. There were 70 cases in whom the Q-Tc was found to have decreased to a value below the average normal plus 1 S.D. There was wide variation in the time intervals following the acute episode at which this lower value was reached (table 2, part a). In the remaining 27 cases, over varying periods of observation, the Q-Tc had not decreased to a value below the average normal plus 1 S.D.; in 7 of these it had remained at a value above the average normal plus 2 S.D. (table 2, part b).

The course of the P-R interval in the 97 cases during follow-up observation was analyzed. Of the patients in whom there had been a single episode of carditis the P-R interval remained prolonged in 6 of the 29 whose Q-Tc value became less than the average normal plus 1 S.D., and also remained prolonged in 3 of the 13 patients whose Q-Tc remained above the average normal plus 1 S.D. Of the patients who were followed after the last of multiple episodes of carditis, the P-R interval remained prolonged in 4 of the 24 whose Q-Tc became less than average normal plus 1 S.D., and also remained prolonged in 1 of 7 patients whose Q-Tc value remained above average normal plus 1 S.D.

TABLE 2

Q-Tc During Inactive Phase

Observations Following 97 Active Rheumatic Episodes During Which Q-Tc Exceeded Average Normal +1 Standard Deviation

A. Cases With Decrease of Q-Tc to Value Below Average Normal +1 S.D.

	No. of Cases	Time of Occurrence									
		Prior to Discharge	Yr.								
			1	2	3	4	5	6	7	8	9
Group I	29	4	10	1	2	4	1	3	3	1	—
Group II	24	—	6	2	5	6	4	—	—	—	1
Group III	5	1	2	—	—	—	1	—	1	—	—
Group IV	11	1	4	1	2	1	—	1	—	1	—
Group V	1	1	—	—	—	—	—	—	—	—	—
Totals	70	7	22	4	9	11	6	4	4	2	1

B. Cases With Q-Tc Remaining at Value Above Average Normal +1 S.D.

	No. of Cases	No. of Yr. of Observation								
		1	2	3	4	5	6	7	8	9
Group I	13	1	2*	3	2	—	1	2*	2	—
Group II	7	1	2*	—	—	—	3*	1	—	—
Group III	2	1*	—	—	1	—	—	—	—	—
Group IV	2	—	1*	—	—	—	—	—	1*	—
Group V	3	—	—	—	—	3	—	—	—	—
Totals	27	3	5	3	3	3	4	3	3	—

* Represents inclusion of single case in which Q-Tc exceeded average normal +2 S.D.

Group I: Cases observed following single episode of carditis.

Group II: Cases observed following last of multiple episodes of carditis.

Group III: Cases observed following episode with prolonged P-R only evidence of carditis.

Group IV: Cases observed following polyarthritis without carditis.

Group V: Cases observed following chorea without carditis.

Course of Q-Tc as observed in 97 patients following acute episode in which Q-Tc had exceeded average normal plus 1 S.D. None of these patients had any clinical or laboratory evidence of rheumatic activity during this follow-up period. In significant number of cases Q-Tc decreased slowly over varying periods of years to value less than average normal plus 1 S.D. In smaller number of cases Q-Tc did not fall below this value during years of observation.

Of the 7 patients observed following an acute episode during which a prolonged P-R interval was the only evidence of carditis, prolongation persisted in 1 of the 5 whose Q-Tc became less than the average normal plus 1 S.D.; the P-R also remained prolonged in 1 of the 2 patients in whom the Q-Tc remained above the average normal plus 1 S.D.

In the patients studied following acute episodes of polyarthritis or chorea with neither clinical carditis nor prolongation of the P-R interval, this value remained within normal range throughout the period of follow-up observation.

TABLE 3

INCIDENCE OF HEART DISEASE PRESENT AT END OF FOLLOW-UP OBSERVATION

Cases in whom Q-Tc value had exceeded average normal +1 standard deviation during active phase

	Total No. of Cases	No Heart Disease	Organic Heart Disease†		
			Mild	Moderate	Severe
Group I. Cases observed after single episode of obvious carditis.					
Q-Tc became less than average normal +1 S.D.	29	12	4	8	5
Q-Tc remained above average normal +1 S.D.	13	5	5**	2	1
Group II. Cases observed after last of multiple episodes of carditis.					
Q-Tc became less than average normal +1 S.D.	24	5	1	6	12
Q-Tc remained above average normal +1 S.D.	7	1	2	2*	2*
Group III. Cases observed after episode with prolonged P-R interval as only evidence of active carditis.					
Q-Tc became less than average normal +1 S.D.	5	4	1	—	—
Q-Tc remained above average normal +1 S.D.	2	1	1*	—	—
Group IV. Cases observed after episode of polyarthritis without carditis.					
Q-Tc became less than average normal +1 S.D.	11	8	3	—	—
Q-Tc remained above average normal +1 S.D.	2	2**	—	—	—
Group V. Cases observed after episode of chorea without carditis.					
Q-Tc became less than average normal +1 S.D.	1	1	—	—	—
Q-Tc remained above average normal +1 S.D.	3	2	1	—	—

† Organic Heart Disease

Mild —Mitral insufficiency and/or aortic insufficiency with minimal cardiac enlargement.

Moderate—Mitral insufficiency and/or aortic insufficiency, mitral insufficiency and stenosis with moderate cardiac enlargement.

Severe —Mitral insufficiency and stenosis, with aortic insufficiency plus or minus stenosis, all with considerable to marked cardiac enlargement.

* Each asterisk represents an individual case in which Q-Tc remained above average normal +1 S.D.

Incidence of heart disease in 97 patients observed subsequent to rheumatic episodes in which Q-Tc had exceeded average normal plus 1 S.D. No intervening rheumatic activity occurred in any of these. Comparison of those in whom Q-Tc became less and those in whom it remained above value for average normal plus 1 S.D. showed no apparent correlation with development or degree of heart disease present at end of observation period.

Incidence of Organic Heart Disease at the End of the Observation Period

It was considered important to evaluate whether there was a difference in incidence of organic heart disease between the cases in whom there had been a decrease in Q-Tc value to below the average normal plus 1 S.D. during follow-up observation and those cases in whom the Q-Tc had remained above this value. The cardiac status present at the end of this period of observation in the Clinic was analyzed from this point of view as shown in detail in table 3.

Among the 29 patients who had had a single attack of carditis following which the Q-Tc became less than the average normal plus 1 S.D. there were 12 without organic heart disease (41%) and 17 in whom definite evidence of organic heart disease was present (59%). Of those 13 patients with a single attack in whom the Q-Tc remained above the average normal plus 1 S.D., there were 5 patients (38%) with no organic heart disease and 8 patients (62%) who had organic heart disease. Although the numbers are small it

would appear that in this group of patients who had only one episode of carditis, there was no significant difference in the development of organic heart disease between those patients in whom the Q-Tc became less than the average normal plus 1 S.D. and those patients in whom it remained above this value during the observation period following the acute episode.

Among the 24 patients who had had more than one attack of carditis and in whom the Q-Tc value became less than the average normal plus 1 S.D. during observation after the last attack, 5 had no organic heart disease (21%) and 19 had definite evidence of organic heart disease (79%). Of the 7 patients in whom the Q-Tc remained prolonged, heart disease was present in all but one patient. From the authors' observations it would seem that the development of organic heart disease is more related to multiple episodes of carditis than to whether the Q-Tc became less than or exceeded the average normal plus 1 S.D. following the last active phase.

Of the patients who had a prolonged P-R interval as the only evidence for carditis, in 5 the Q-Tc became less than the average normal plus 1 S.D., and in 2 it exceeded this value during the inactive phase. In these 5 patients there was no organic heart disease in 4, while in one organic heart disease was present. Of the 2 patients in whom the Q-Tc remained above the average normal plus 1 S.D., one had organic heart disease and the other had mild organic heart disease.

Thirteen patients who had polyarthritis without carditis were followed; in 11 the Q-Tc became less than the average normal plus 1 S.D. Eight of these 11 patients had no organic heart disease and 3 had definite though minor evidence of organic heart disease without there having been any clinical evidence of intervening rheumatic activity. There was no evidence of organic heart disease in the 2 patients whose Q-Tc remained prolonged.

Among the patients who had had chorea, in 4 the Q-Tc exceeded the average normal plus 1 S.D. during the acute episode. In 3 the Q-Tc remained above this value during observation, and in one it returned to average normal. One patient whose Q-Tc remained prolonged developed signs of slight mitral insufficiency.

Discussion

Although prolongation of the Q-T interval has frequently been observed during acute rheumatic carditis, there is lack of agreement in various reports as to the incidence of this occurrence and as to its value as an index of rheumatic activity. As there is no readily apparent single cause for the discrepancies between reported series, several possible factors should be considered. The type of electrocardiographic instrument employed, and the inherent difficulty of accurate delineation of the Q-T interval in certain records may be of some importance. Individual differences in methods of measurement among observers is possibly of significance. In this respect it has been recommended that each observer analyze a series of ECGs from normal subjects to obtain his own standard of reference, and that the interpretation of findings in patients studied be made in the light of the individual observer's series of normal controls.

Aside from differences in methods of measurement, variation in clinical criteria used in making the diagnosis of active rheumatic carditis, as well as the inclusion of cases having pericarditis with effusion or cases in congestive failure treated with digitalis, may have influenced the findings in some of the series. Another factor postulated is the possible influence on the Q-Tc of changes in acid-base relationship, due either to the clinical

condition of the patients or the effect of drugs employed. There is insufficient data at this time to evaluate the importance of this latter factor; more extensive studies along this line are needed.

Still another factor in deciding as to the abnormality of an observed value of the Q-Tc is the figure chosen for the upper limit of normal. The average normal value plus two standard deviations includes 95% of cases in a normal distribution. In analyzing the discrepancies between various series, it is important to take into account whether the average plus one standard deviation or plus two standard deviations is the value accepted by the individual authors as the upper limit of normal. In the most recent series of normal children reported by Alimurung et al.,[8] the average plus two standard deviations was used in setting the upper limit of normal.

In the material presented the figure for the average normal plus two standard deviations as obtained from the normal control group is used as reference for the upper limit of normal. This value is 0.450. The Q-Tc exceeded this value in 3.8% of the normal cases, in 69% of the patients with active carditis, in 38.5% of the patients with other electrographic evidence for carditis, in 50% of the patients with polyarthritis, and in 17% of the patients with chorea. If the value for the upper limit of normal is taken as the average plus one instead of two standard deviations the incidence of prolongation of the Q-Tc is of course greater.

The Q-Tc was usually prolonged during obvious active rheumatic carditis in the series. The findings of prolongation of the Q-Tc in some cases of polyarthritis and of chorea without clinically evident active carditis suggests that in certain of these instances a mild degree of subclinical carditis was present. The higher incidence of a prolongation of the Q-Tc as compared with the P-R interval in this material would seem to indicate that the former may be more closely correlated with rheumatic activity than the latter.

On follow-up of the 97 patients whose Q-Tc values had exceeded the average normal plus one standard deviation during their acute illness, a certain number maintained a prolonged Q-Tc value during the period of subsequent observation. If the upper limit of normal is taken at one standard deviation, in 27% of the patients the Q-Tc remained prolonged, and if the upper limit is taken at two standard deviations, the Q-Tc remained prolonged in 7% of the patients. It should be noted that the corresponding figures for the normal cases are 12.7% and 3.8%, respectively. Of the 45 patients who had had a prolonged P-R interval during the active phase, it remained prolonged in 16 (35.5%). The above values were persistently prolonged without clinical or laboratory evidence of continued rheumatic activity. Furthermore the development of organic heart disease or progression in previously established heart disease did not occur in this group in whom the Q-Tc remained persistently prolonged. It was of interest that usually persistent prolongation of the Q-Tc and P-R interval did not occur concomitantly.

The significance of these findings in the authors' opinion is that the persistence of prolonged Q-Tc does not necessarily indicate continued rheumatic activity leading to a higher incidence of subsequent organic heart disease.

Summary and Conclusions

The Q-Tc in 79 normal children ranging in age from 2 to 12 years was found to be 0.418 with a standard deviation of 0.016.

The Q-Tc was studied in 208 children ranging in age from 3 to 13 years during active rheumatic fever and chorea. One hundred nineteen of these patients were subsequently

followed in the cardiac clinics. The P-R interval was studied simultaneously, and observations were made in regard to the presence or absence of resultant organic heart disease.

A significant number of patients showed prolongation of the Q-Tc value during the acute illness, far more so in those with rheumatic carditis than with polyarthritis or chorea alone. During the inactive phase, a number of patients maintained a prolonged Q-Tc value.

The Q-Tc value in patients with rheumatic fever is an additional laboratory aid which may help in determining the presence of active carditis. The prolongation of the Q-Tc value in polyarthritis and in chorea in the absence of other clinical findings should suggest further observation for the possible presence of a mild carditis. However, in evaluating patients whose Q-Tc is above normal and in whom the presence of active carditis is otherwise questioned, consideration must be given to the fact that the Q-Tc has been found to exceed the upper limit of normal in some normal children.

These findings show that, following active rheumatic fever, in some patients the Q-Tc value may remain prolonged over long periods of time in the absence of any manifest clinical activity or change in the cardiac status of the patient. Therefore it is the opinion of the authors that when careful evaluation over a period of time shows no other clinical or laboratory evidence of rheumatic activity, the sole finding of a Q-Tc remaining above normal range should not be considered as indicative of persistence of active carditis.

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Taran, L. M., and Szilagyi, N., Rheumatic disease in children, Brit. Heart J. **13**:10, 1951.

Solomon, N. H., and Zimmerman, M., Q-Tc interval of electrocardiogram in rheumatic carditis in children, Am. J. Dis. Child. **81**:52, 1951.

SPANISH ABSTRACT

Intervalo Q-T

Este artículo reporta un estudio del segmento Q-Tc de los electrocardiogramas tomados durante 249 episodios de fiebre reumática aguda de los cuales en 169 se identificó una carditis reumática evidente, en 13 casos, en los que la única prueba de carditis era la prolongación del intervaldo P-R, en 20 con poliartritis y 47 con corea como únicas manifestaciones de proceso reumático. Además, en 97 de los pacientes, se hizo el análisis de los valores de Q-Tc durante un período de observación que varió de 1 a 9 años y que durante su proceso reumático agudo habían tenido un valor Q-Tc mas alto que el promedio normal mas una desviación standard.

En 79 controles normales el valor promedio de Q-Tc fué de 0.418 con una desviación standard de 0.016. Si se toma como límite superior de normalidad el promedio normal más 2 desviaciones standard (0.450) se encontró que Q-Tc excedió este valor en el 69% de los episodios agudos de carditis, en el 38.5% de los episodios agudos de los enfermos cuya única evidencia de carditis fué la prolongación del intervalo P-R, en el 50% de los casos con poliatritis y en el 17% de los pacientes con corea. Por consiguiente, se infiere que la mayoría de enfermos con carditis activa tendrán un Q-Tc prolongado y que en aquellos pacientes con poliatritis o corea en los cuales no haya otra manifestación clínica de carditis, el hallazgo de un segmento Q-Tc prolongado sugiere que existe un grado ligero de carditis.

A continuación de los períodos de actividad reumática evidente Q-Tc decreció, en tiempo más o menos variable, a valores menores que el promedio normal mas una desviación standard, en 70 de los 97 enfermos en los cuales Q-Tc había excedido este nivel durante el proceso agudo. En 7 enfermos Q-Tc permaneció arriba del promedio normal más dos desviaciones standard.

Concluyendo, estos hallazgos demuestran que después de una fiebre reumática aguda algunos enfermos continúan presentando el segmento Q-Tc prolongado por largos períodos de tiempo, en ausencia de manifestación clínica alguna de actividad o cambio en las condiciones cardiacas del paciente. Por lo tanto, si Q-Tc permanece por arriba de los límites de lo normal no debe considerarse como indicación de carditis activa persistente.

Tampoco hubo relación alguna entre la frecuencia con que se registró lesión orgánica del corazón al final del período de observación de este grupo de enfermos y la evolución que sufrió Q-Tc durante el período de observación correspondiente a la fase de inactividad reumática.

76 Chester Avenue, Brooklyn

SULFOBROMOPHTHALEIN SODIUM EXCRETION TEST AS A MEASURE OF LIVER FUNCTION IN PREMATURE INFANTS

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THE nature, extent and duration of hepatic immaturity in premature infants have been studied in 35 subjects of varying ages and weights by means of the serial sulfobromophthalein sodium [bromosulphalein (BSP)®*] dye excretion test. To the authors' knowledge this test has never been used as a measure of liver function in premature infants although it has been applied in newborns.[1-4]

The test is nonphysiologic in the sense that the liver is not normally called upon to remove the dye from the blood, but is, nevertheless, a true measure of hepatic excretory capacity. It is a sensitive indicator of hepatic dysfunction often antedating the appearance of clinical manifestations.[5-7] Unlike the newly developed flocculation and turbidity tests, the bromsulphalein test does not depend upon levels of plasma protein and phospholipid fractions. In the premature infant, aberrations of these levels are likely to be extrahepatic in origin and hence not true reflections of liver function.

Previous studies of liver function in premature infants have yielded normal values or, where abnormal, have not necessarily indicated hepatic dysfunction. It has been assumed that the hepatic immaturity observed neonatally in infants born at term, as indicated by the degree and duration of physiologic hyperbilirubinemia, is exaggerated in those born prematurely.[8-10] The hypoproteinemia of prematurity, which has also been ascribed to hepatic immaturity,[11] results largely from low values for the globulin fraction,[12,13] the major portion of which arises within the reticuloendothelial system and not exclusively in the liver.[14] Because of the alteration of serum cholesterol in liver disease, the cholesterol ester fraction is regarded as a valuable index of hepatic function.[15] Cholesterol values in premature infants are low, however, as in full term infants; they are not correlated with the degree of prematurity, and are thought rather to be related to maternal estrogenic influences and not to any disturbance of liver function.[16] The thymol turbidity test in prematures as well as normal newborns gives values considerably lower than those of normal adults[17,18] probably because of the lower concentration of serum globulins[19,20] and phospholipids.[21-23] The cephalin-cholesterol flocculation test is highly positive in normal newborns[17] and in prematures[24] although the nature of the disturbance in these in-

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* Brand of sulfobromophthalein sodium manufactured by Hynson, Westcott, and Dunning, Inc., Baltimore.

fants is obscure. Hepatic immaturity has been implicated as a cause of the hypoprothrombinemia of prematurity.[11] The neonatal decline in plasma prothrombin can, however, be prevented by the administration of vitamin K.[25, 26] This conversion of vitamin K to prothrombin is a far more accurate test of liver function than the determination of plasma levels alone,[27] and is normal in prematures.

The BSP excretion test measures hepatic excretory ability when the blood is presented with a foreign substance. Elimination of BSP from blood is effected largely by the liver. The rate of removal of dye is controlled by the rate of delivery to the liver, or blood flow, and the efficiency of extraction. The latter depends upon the anatomic relation between the liver cells and the sinusoidal blood stream, and the ability of these cells to remove the dye from the zone of uptake and to excrete it into the biliary system.

In the premature infant, any or all of these factors in the mechanism of BSP elimination may be functioning poorly. The present study establishes that there is indeed an alteration in the handling of BSP by the premature and that such alteration is a function of age, not weight or organ mass.

Method

After drawing an initial blood specimen to obtain BSP-free plasma for the colorimeter blank, 5 mg./kg. of body weight of BSP in 0.5% solution were injected into a scalp vein. The solution was made by diluting one part of the standard test material, containing 50 mg./cc., with 9 parts of distilled water. Serial blood samples were then drawn from other veins at intervals of 3, 8, 15, 30, 45 and 60 min. In some patients, additional specimens were obtained at 2, 4 and 18 hr. It was not always possible to secure all the samples at each of the stated intervals but sufficient values were obtained to permit reasonable interpolation in these cases.

The BSP determinations were performed by a method previously described.[28] Blood was collected, using heparin as an anticoagulant, and after centrifugation, the clear plasma supernate was removed. Plasma proteins were precipitated by addition of an equal volume of acetone. After cooling the mixture and subsequent centrifugation, the supernate was again separated. The purple color of the dye was developed by the addition of 0.1 to 0.2 cc. of 10% sodium hydroxide, and its intensity estimated in the microcolorimetric unit of the Evelyn photoelectric colorimeter, using a 580 millimicron filter.

Gaebler[29] has demonstrated that by the use of the photoelectric instrument it is possible to estimate BSP levels accurately when the plasma is turbid, icteric or hemolyzed. This is of some importance in this study because of the presence of neonatal physiologic hyperbilirubinemia in some of the subjects, and because of the excessive hemolysis which occurs in newborns when the erythrocytes are allowed to stand in their own plasma.[30] To reduce the possibility of error created by the presence of large concentrations of pigment resulting from hemolysis, each plasma sample served as its own control before alkalinization.

Interpretation of the BSP Test

Following a single intravenous injection of BSP into normal adults, a constant proportion of dye is removed from the blood per unit time. The amount removed is a function of plasma concentration and when the logarithms of the plasma BSP values are plotted against time they tend to assume a straight line relationship. At low plasma concentration removal of dye proceeds more slowly and its disappearance from blood, when graphed in the same manner, becomes curvilinear.[31, 32] This is thought to be caused by a decreased uptake of BSP by the liver,[33] a phenomenon spoken of as "saturation." When flattening of the excretion curve, or "saturation," occurs early and while plasma BSP is still high, liver function is abnormal. In some patients with hepatic disease, the first part of the curve may be a sharp slope characteristic of initial rapid removal of BSP, as is seen in normals, followed by early flattening while at high plasma dye concentration indicating

a slower and decreasing rate of removal. In other disorders, the removal rate may be constant but quite slow from the start yielding a line which, while straight, is more nearly horizontal than normal.

To illustrate the above considerations and to provide a frame of reference for the analysis of the data obtained in the premature infants, the excretion curves of two normal adults (A, B) and three patients with hepatic disease (C, D, E) are shown in chart 1. The same dosage schedule of 5 mg./kg. of body weight was maintained, but for the adults the standard 5% BSP solution was used. In both normal adults (A, B) the plotted values are rectilinear for the greater part of the test. After 45 and 30 minutes, respectively, and at low plasma concentrations they become curvilinear. Lines C and E are the

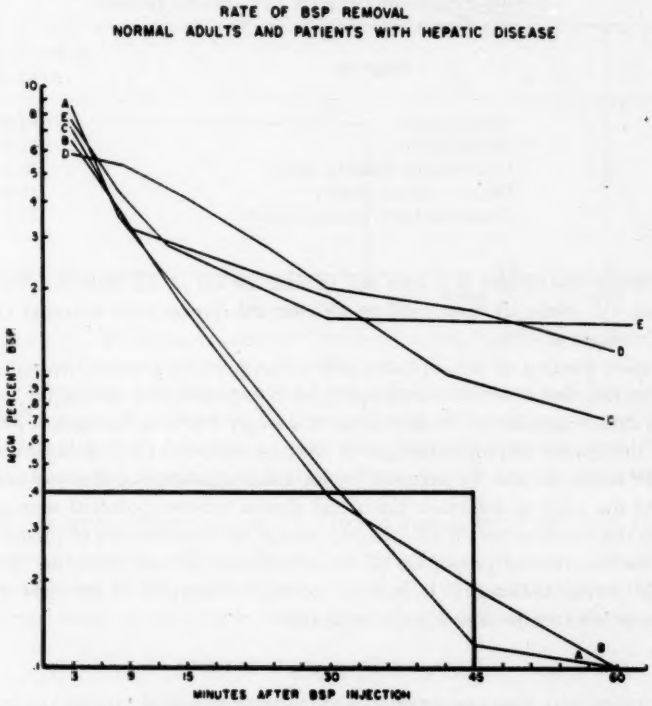

CHART 1. BSP excretion curves in 2 normal adults (A, B) and 3 patients with hepatic disease (C, D, E).

excretion curves of an adult with postinfectious hepatitis and an infant with congenital luetic hepatitis, respectively, and illustrate the biphasic type of curve discussed above. The curve obtained in a patient with cirrhosis is shown in line D and represents a gross distortion of the normal.

As commonly performed in clinical practice the end point of the test is the percentage of dye retained in the blood 45 minutes after a single intravenous injection of BSP 5 mg./kg. body weight.[34] To standardize the interpretation of the test, it is assumed that

the plasma volume is 50 cc./kg. body weight and that, therefore, at the point of uniform dispersion of dye a concentration of 10 mg./100 cc. of plasma is achieved. This is arbitrarily designated as 100%. A retention of 4% or less is regarded as normal.[6] Thus the calculations are based on two assumptions, both of which are open to question. It is unlikely that all subjects in whom the test is performed have identical plasma volumes.[35] It is also unlikely that homogeneous diffusion of dye in plasma occurs before actual removal by the liver begins. The failure to calculate the dosage of BSP on the basis of the actually determined plasma volume is thus a potential source of considerable inaccuracy in the 45 minute retention test.

TABLE 1

NORMAL ADULTS AND PATIENTS WITH HEPATIC DISEASE

	Diagnosis	% BSP Retention at 45 min.
A	Normal adult	1.2
B	Normal adult	1.8
C	Postinfectious hepatitis (adult)	10.3
D	Hepatic cirrhosis (adult)	17.0
E	Congenital luetic hepatitis (infant)	15.6

From chart 1 and table 1 it is seen that in both normal adults retention at 45 minutes is less than 4% while all three patients with hepatic disease have retention values considerably in excess of 10%.

The graphic plotting of serial plasma BSP values provides a more dynamic evaluation of liver function and a better understanding of hepatic efficiency during the progression of the test than is possible by the estimation of a single BSP concentration at a fixed time. Also, for the usually employed dosages of dye, the utilization of the logarithms of the plasma BSP levels obviates the necessity for the exact calculation of dose per unit of body weight and the need to determine the actual plasma volume, potential sources of error inherent in the standard test. With changing dosage the concentration of plasma BSP may vary but since a constant proportion of dye is removed per unit time, the slope of the line should remain unchanged. It may, of course, be displaced to the right or left depending upon whether the dose is larger or smaller.

DATA ON PREMATURE INFANTS

BSP excretion tests were performed in 35 premature infants of varying age and weight. The infants are divided into five groups according to age at the time the tests were performed. Within each of the groups the excretion curves are numbered in order of increasing weight except for those infants 42 days and over whose curves are numbered in order of increasing age. The tables list the same subjects identified to correspond with their respective excretion curves and show individual birth weights, weights at the test, age and percentage dye retention at 45 minutes.

A. Premature Infants 18 to 28 Hours of Age (chart 2 and table 2)

These seven prematures weigh 1490 to 2350 gm. The curves, with the exception of number 7, from whom only three values could be obtained, are similar to those shown

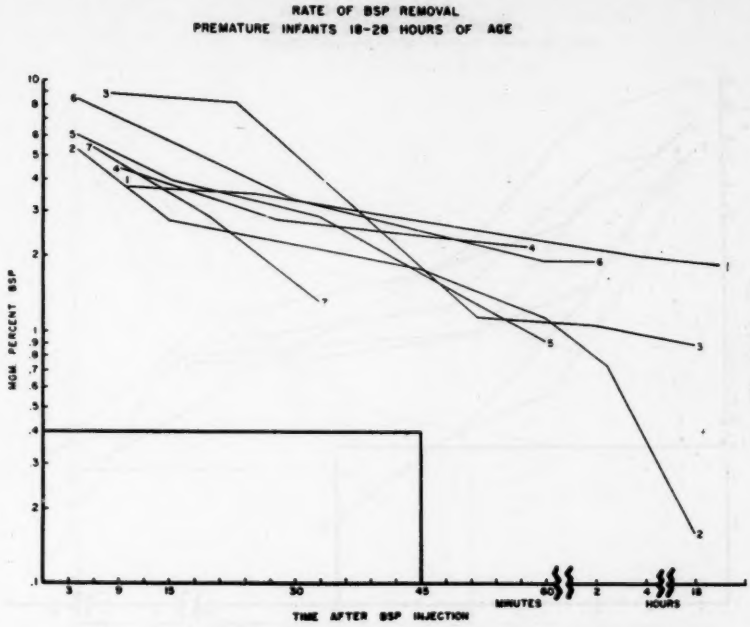

CHART 2. BSP excretion curves in 7 premature infants 18 to 28 hr. of age.

in chart 1 for patients with hepatic disease but differ in the absence of the initial phase of rapid BSP removal. The slopes of the lines with early flattening indicate decidedly slow and decreasing rates of BSP clearance. Six of the prematures have more than 17% retention at 45 minutes and four have high plasma levels 4 to 18 hours after injection.

B. Premature Infants 1½ to 3½ Days of Age (chart 3 and table 3)

These seven prematures weigh 1570 to 2200 gm. Five of the seven have retention at 45 minutes in excess of 9% and the three in whom the test was extended to 18 hours still have moderate retention at this time. While generally the curves are abnormal when com-

TABLE 2

PREMATURE INFANTS 18 TO 28 HOURS OF AGE

	Birth wt. (gm.)	Age (hr.)	% BSP Retention at 45 min.
1	1490	28	27.5
2	2035	28	18.2
3	2050	26	18.3
4	2125	18	24.0
5	2130	28	17.2
6	2210	20	25.5
7	2350	24	—

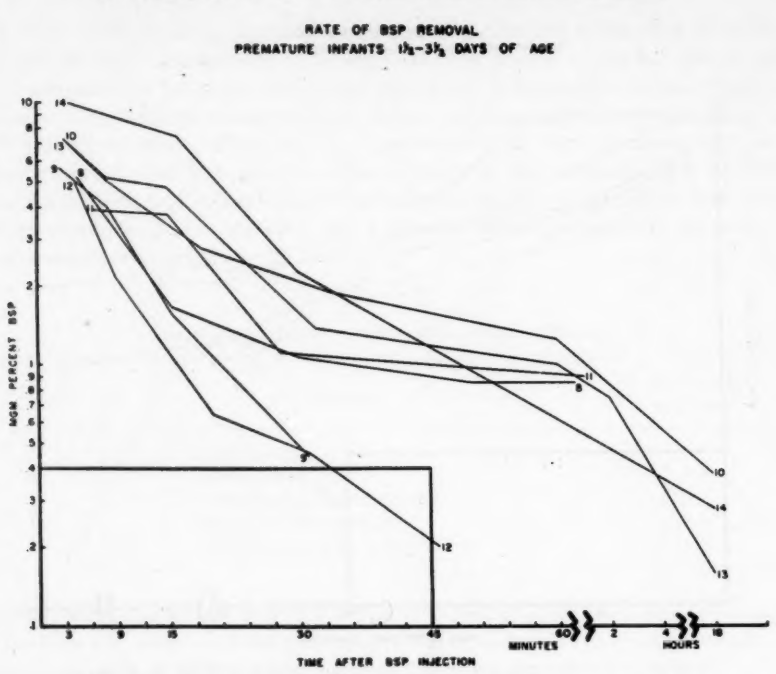

CHART 3. BSP excretion curves in 7 premature infants 1½ to 3½ days of age.

pared to those of adults and show early flattening at high plasma BSP concentration, several are now biphasic and show the initial phase of rapid dye removal.

C. Premature Infants 4½ to 14 Days of Age (chart 4 and table 4)

In this group of five infants four are 4½ to 6 days of age and one, subject 19, is 14 days. The weights vary from 1575 to 2150 gm. Four show the initial sharp slopes of rapid BSP clearance. However, early flattening at fairly high plasma BSP levels is still present in three. Subject 19 has a curve approaching normal and it seems certain that

TABLE 3

PREMATURE INFANTS 1½ TO 3½ DAYS OF AGE

	Birth wt. (gm.)	Age (hr.)	Wt. at Test (gm.)	% BSP Retention at 45 min.
8	1570	62	1510	9.0
9	1930	72	1790	<4.0
10	1830	62	1810	15.5
11	2150	84	1900	11.8
12	2140	48	2000	2.1
13	2150	60	2000	11.8
14	2260	42	2170	—

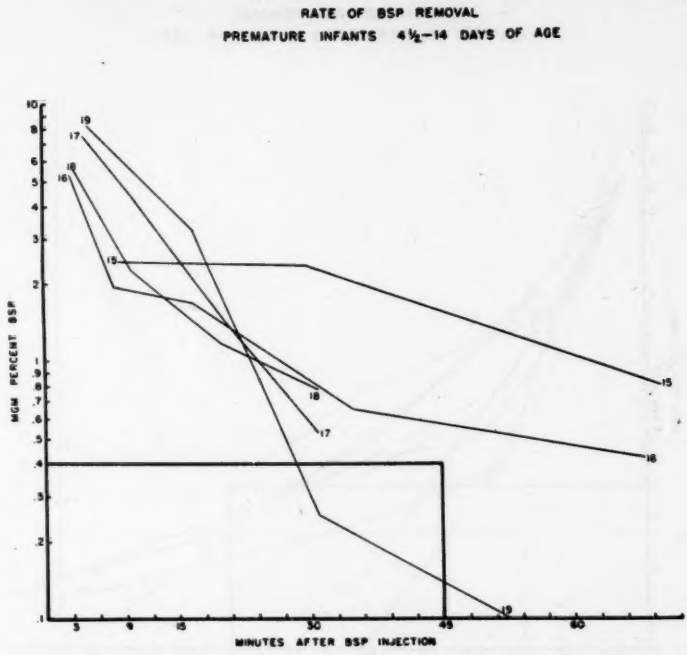

CHART 4. BSP excretion curves in 5 premature infants 4½ to 14 days of age.

subject 17, each of whose values approximate a straight line, would have had a normal curve had more blood samples been secured for analysis. The percentage dye retention at 45 minutes is also approaching adult values.

D. Premature Infants 21 to 32 Days of Age (chart 5 and table 5)

These 10 prematures weigh 1870 to 2750 gm. In all there is now rapid initial removal of dye as shown by the sharp slopes of the curves and all have retention values of less than 4% at 45 minutes. The trend toward the normal adult configuration continues but the biphasic character of the curves is still apparent in most. Early flattening is still present but the plasma concentration at which this now occurs is approaching normal. It is appar-

TABLE 4

PREMATURE INFANTS 4½ TO 14 DAYS OF AGE

	Birth wt. (gm.)	Age (days)	Wt. at Test (gm.)	% BSP Retention at 45 min.
15	1660	4½	1575	15.5
16	1720	4½	1645	5.7
17	2070	6	1875	<5.0
18	1980	5	1990	—
19	1970	14	2130	1.4

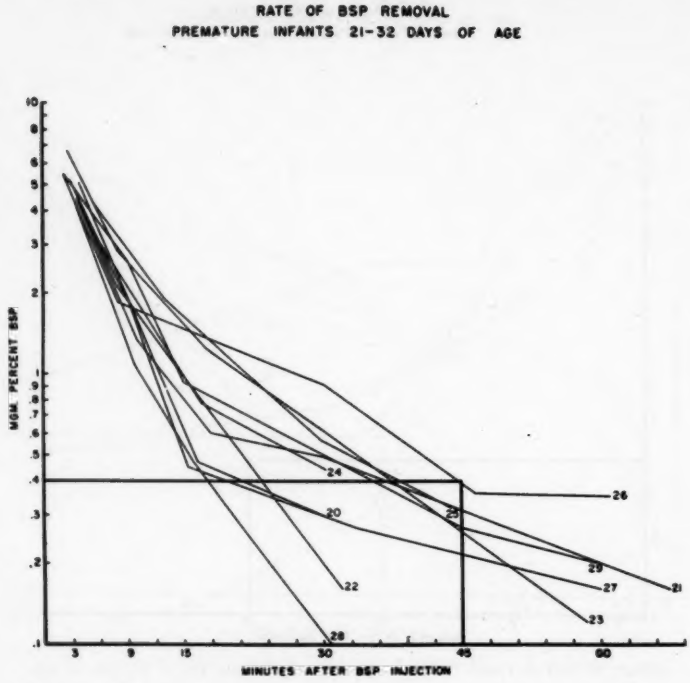

CHART 5. BSP excretion curves in 10 premature infants 21 to 32 days of age.

ent that in most of these infants hepatic clearance of BSP is less efficient than in the adult although if the adult standard 45 minute retention of 4% is the criterion, all are normal.

TABLE 5

PREMATURE INFANTS 21 TO 32 DAYS OF AGE

	Birth wt. (gm.)	Age in Days	Wt. at Test (gm.)	% BSP Retention at 45 min.
20	1530	27	1870	1.8
21	1680	27	1940	3.0
22	1700	32	1980	0.0
23	2030	22	2160	3.8
24	1870	26	2260	<4.0
25	1980	21	2330	3.0
26	1970	27	2400	3.9
27	2210	28	2490	2.1
28	2070	24	2630	0.0
29	2120	26	2750	2.7

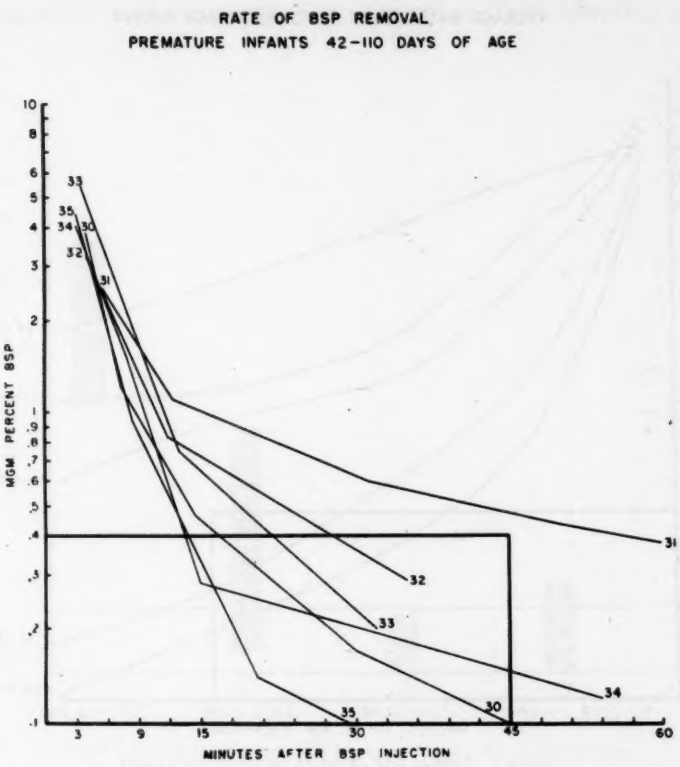

CHART 6. BSP excretion curves in 6 premature infants 42 to 110 days of age.

E. Premature Infants 42 to 110 Days of Age (chart 6 and table 6)

The weights of these six infants range from 2010 to 4120 gm. With a single exception all have normal retention values at 45 minutes. The curves are still biphasic with "saturation" occurring above normal adult levels in all except those over 68 days of age.

TABLE 6

PREMATURE INFANTS 42 TO 110 DAYS OF AGE

	Birth wt. (gm.)	Age in Days	Wt. at Test (gm.)	% BSP Retention at 45 min.
30	1845	42	2530	0.0
31	1530	50	2145	4.8
32	990	68	2010	<3.0
33	1070	68	2270	2.0
34	980	93	2650	1.5
35	1430	110	4120	0.0

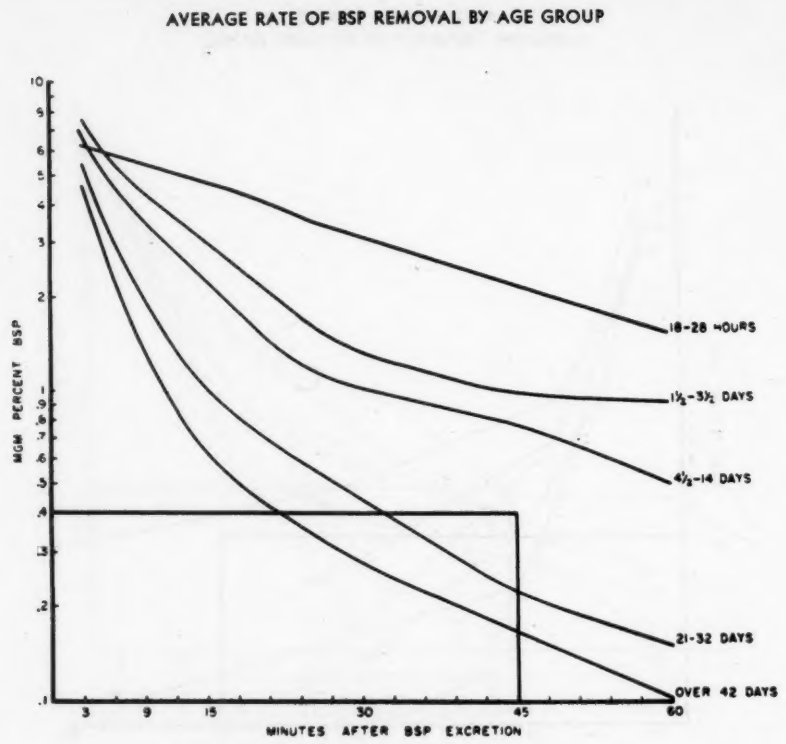

CHART 7. Average BSP excretion curves by age groups.

The result of the BSP tests may now be considered as a whole. In chart 7 are depicted the average excretion curves in each of the aforementioned age groups. The progressive improvement in hepatic clearance is apparent at once. With increase in age the rate of BSP removal increases and hepatic efficiency presumably improves. The initial part of the curves shows a trend toward more nearly vertical slopes; flattening becomes less apparent, and occurs at lower plasma levels with advancing age.

That age is the determining factor in the maturation of hepatic function, as measured by the BSP test, may be seen also by a comparison of individual excretion curves. Thus, subjects 5 and 19 both weigh 2130 gm. The former is 28 hours of age and has a grossly abnormal curve; the latter is 14 days and has a curve approaching the normal pattern. It might be expected that a newly born premature infant would have poorer liver function than an older infant of lesser weight. Comparison of the curves of subjects 7 and 20 substantiates this. The excretion curve of subject 20 who is 27 days of age and weighs 1870 gm. is distinctly superior to that of subject 7 who is 2350 gm. but only 24 hours of age. However, this is not invariably so. For example, subject 12 who is 48 hours old and weighs 2000 gm. has a superior excretion curve to that of subject 18 whose weight is identical but who is 5 days of age. It must be pointed out, however, that subject 12 has a greater birth weight and was presumably more mature at the time of birth.

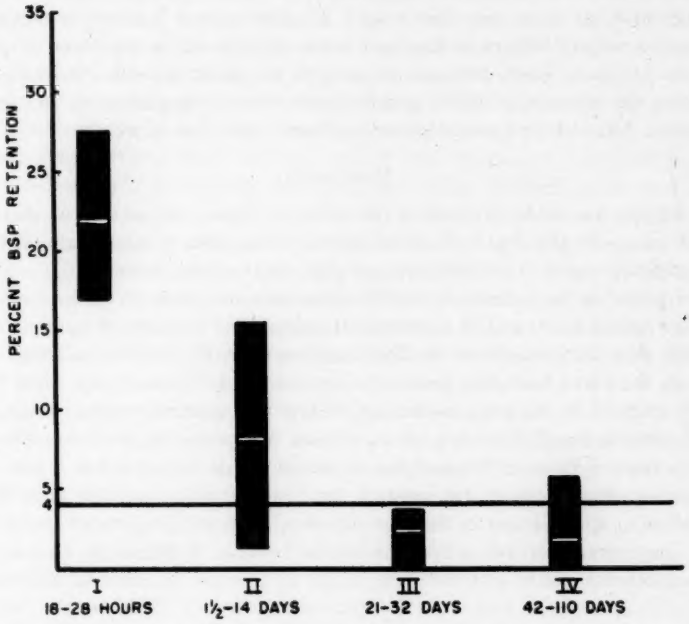

CHART 8. Average and range of BSP retention at 45 min. by age groups.

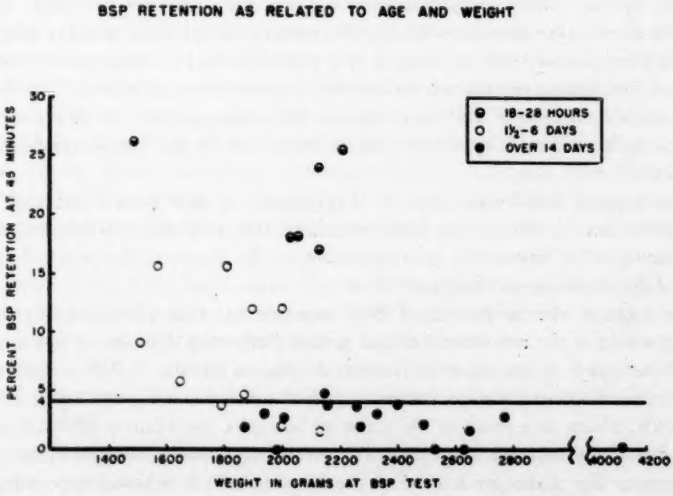

CHART 9. BSP retention at 45 min. as related to age and weight.

Chart 8 shows the range and the average BSP retention at 45 minutes by age group. It is clear that by three weeks after birth adult levels are reached.

In chart 9 the percentage retention values at 45 minutes are plotted against weight by age. For all the tests performed, improvement in hepatic function appears to correlate primarily with age rather than with weight. Thus the infants from 1½ to 6 days of age, all of whom weigh 2000 gm. or less, have better retention values than those of one day of age, most of whom weigh 2000 gm. or more. In the group of infants weighing 1800 to 2000 gm., the retention of BSP is greater in the very young prematures and less in the older ones. After 14 days normal values are found regardless of weight.

Discussion

No attempt was made to correlate the extent of hepatic immaturity, as measured by the BSP test, with the degree of bilirubinemia. It has already been established that no such correlation exists in the newborn and that abnormal dye retention can occur in the neonatal period in the presence of normal serum bilirubin levels.[1, 3, 4] It has been demonstrated in normal adults and in experimental animals that injection of bilirubin does not materially alter the character of the BSP excretion curves.[33] Bilirubin and BSP are both carried in the blood bound to protein.[36] Cantarow et al.[37] believe that while both are probably excreted by the same mechanism, BSP is preferentially excreted when they are injected simultaneously. This lack of parallelism had previously been noted by others. Snell, Greene and Rowntree[38] found that obstruction of the biliary system is not followed by immediate impairment of dye removal. Later, dye retention parallels bilirubin retention. Following the injection of BSP and bilirubin, Mills and Dragstedt[39] found that the rate of disappearance of dye exceeds that of the bilirubin. Furthermore, blocking of the reticuloendothelial system with india ink results in a greater retention of BSP than bilirubin.

Investigators are not in accord as to the exact mechanism by which BSP is removed from the blood and excreted into the bile. Herlitz[1] originally suggested that BSP was taken up by the reticuloendothelial system, principally the Kupffer cells. Subsequent studies by others have demonstrated that the removal of dye from blood is delayed when the reticuloendothelial cells are blocked by a prior injection of india ink or when a large volume of functioning reticuloendothelial cells is removed by splenectomy.[39, 40] Eviscerated animals are able to remove BSP from blood in the absence of the liver and a considerable amount may be removed by the peripheral tissues under the special conditions of the experiments.[41, 42]

On the basis of differential rates of disappearance of BSP from blood and its subsequent appearance in bile, it has been postulated that two separate mechanisms, which can be shown to be dissociated, are responsible for the phases of dye removal on the one hand, and dye excretion on the other.[43, 44]

One concept of the mechanism of BSP excretion has been formulated by those who support the role of the reticuloendothelial system. Following diffusion of dye into plasma, where it is bound to the albumin fraction of plasma protein,[45] BSP is removed from blood by the reticuloendothelial system, largely the Kupffer cells, and transferred to the hepatic cells, where, as a result of the action of bile salts, the albumin-BSP link is broken, and the dye finally excreted into bile.[43] The precise mechanism involved in these changes is not known. The scavenger activity of the Kupffer cells is believed responsible for the early phase of rapid dye removal from blood and the activity of the hepatic cells accounts

for the slower phase of excretion of BSP into bile. It is possible for biliary excretion to be abnormal while removal of dye from blood proceeds normally. On the other hand, if excretion of BSP into bile is delayed by parenchymal disease, transfer of BSP from Kupffer cells may be delayed. Hence the rate of further uptake of dye from blood by the Kupffer cells may then be reduced. It is probably the delay in biliary excretion which produces the flattening of the curves or "saturation" seen in patients with liver disease in chart 1.

The role of the reticuloendothelial cells in this concept is not universally accepted. Ingelfinger and his colleagues[32] believe that the removal of a constant proportion of dye in normal subjects speaks for a single mechanism or at least a predominant mechanism. Brauer and Pessotti,[45] as a result of *in vivo* and *in vitro* experiments, have postulated that the basic mechanism is an exchange of protein-bound BSP between plasma and hepatic cells. Mendeloff and his coworkers[33] have shown, by simultaneous measurements of BSP in peripheral and hepatic venous blood, that "saturation" is always associated with a decrease in BSP extraction by the liver. They concluded that "saturation" is caused by an impairment of the hepatic uptake mechanism. They also challenged the validity of the evidence bearing on the role of the reticuloendothelial system in removing BSP from blood in animal experiments involving splenectomy and india ink injections. Splenectomy may affect the uptake of BSP by reducing portal circulation. India ink may also block the sinusoids thereby preventing sufficient contact between parenchymal cells and blood.

While Kauhtio[46] has observed dye in both parenchymal and Kupffer cells in frozen sections of the liver in test animals, the weight of physiologic evidence would appear to favor the view that in the handling of nonparticulate or soluble dyes, the reticuloendothelial system has no direct share. All workers are generally agreed that under the conditions of the clinical test as usually performed, the liver is the principal site of BSP removal and excretion.

In order to explain the altered liver function of prematures, it is necessary to invoke all facets of the mechanism of BSP excretion. These include hepatic blood flow, rapidity of uptake of BSP, and efficiency of excretion of dye into bile by the parenchymal cells.

In a test that involves clearance of a dye from blood by the liver, hepatic blood flow is an important factor. Under circumstances of impaired circulation, as in shock or cardiac failure, decreased removal of BSP results.[47] It is possible that the markedly flattened curves indicative of slow dye removal seen on the first day of life result from the adjustments in circulation which take place immediately after birth. It is unlikely, though, that this would explain hepatic dysfunction lasting for some time thereafter. The closure of the ductus venosus cannot conceivably have anything but a transient effect since it closes as a consequence of the cessation of blood flow from the umbilical vein. The portal venous and hepatic arterial flow are intact, function normally, and carry the burden of the circulation.

On the other hand, it has been shown that there is progressive increase in the number of capillaries in the liver with increasing fetal age[48] and it may well be that this improvement in vascularity, by increasing the effective hepatic blood flow and thereby exposing the parenchymal cells to a larger volume of blood in the sinusoids, leads to improved efficiency of dye removal. Fig. 1 shows this increase in capillaries in the livers of fetuses of varying weights.

The logarithmic decline observed in the very young premature infants suggests that, in these subjects, circulation is the limiting factor, and that for a while, excretion can keep pace with the rate of delivery of BSP to the liver. This is in keeping with the anatomic

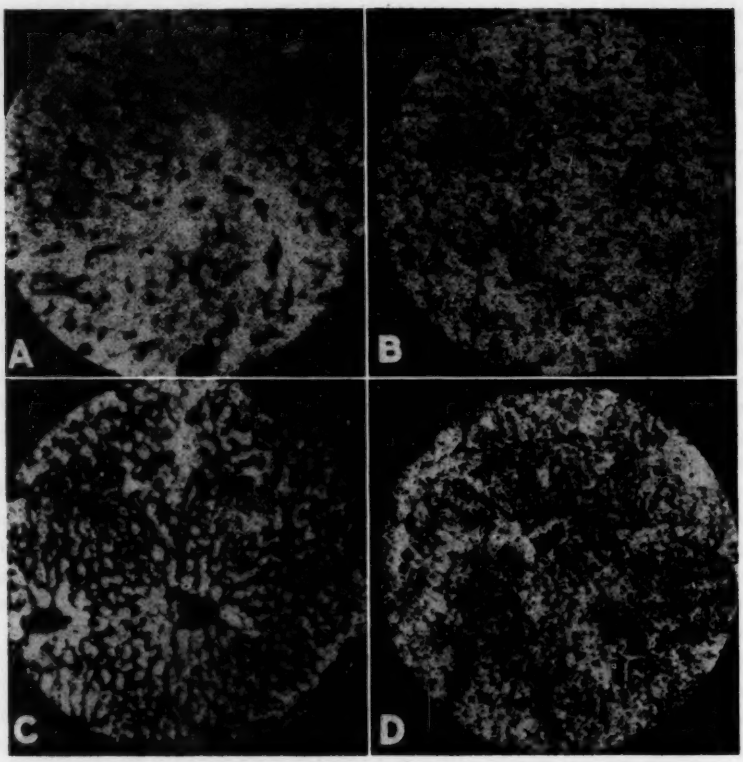

FIG. 1. Photomicrographs showing progressive increase in capillary vascularity of liver in neonates of varying weights: A. in infant weighing 800 gm.; B. in infant weighing 1080 gm. C. in infant weighing 2020 gm. and D. in infant weighing 3730 gm. (Courtesy, Mali and Räiha,[48] Acta Paediatrica).

handicap of relatively incomplete capillary vascularity. Examination of the excretion curves indicates that the first sign of approaching normalcy is the appearance of the sharp initial slopes indicating rapid hepatic clearance of dye early in the course of the test. This may result from the increase in capillaries leading to an improved sinusoidal blood flow, or to a maturation of the hepatic uptake mechanism. The continuance of the biphasic character of the curves, by analogy with the adult, suggests an incompetent excretory mechanism which results in early "saturation" of the hepatic parenchyma so that further removal of dye from blood is impaired.

The disappearance of BSP from the blood stream of the premature infant differs from that of the normal adult in that it occurs at a much slower rate. As seen previously in chart 7, BSP extraction approaches normal with increasing age. The curves become more nearly vertical, the initial slope becomes sharper, and "saturation" occurs at progressively lower plasma BSP levels. Even at 6 to 8 weeks, however, biphasic elimination curves are obtained which resemble those seen in adults with hepatic disease. For more critical interpretation of these data it is necessary to secure information concerning quantitative excretion of dye into bile as compared with the amount of BSP removed from blood, and the percentage

extraction of dye from the blood traversing the liver. Technical difficulties preclude obtaining these measurements in prematures.

The 45 minute retention values obtained in the prematures clearly indicate that there is a close correlation between these results and the age, rather than the weight, of the infants, and that by three weeks, normal adult values are obtained. While the 45 minute retention figures are normal by three weeks, the excretion curves are distinctly biphasic for a longer period and did not achieve the adult pattern until after 68 days in this study. Thus, the excretion curve is a far more sensitive indicator of hepatic function than is the determination of the single 45 minute plasma BSP level.

While there is no correlation between efficiency of BSP clearance and the weight of the premature infant there is also no correlation with organ mass. Thus, if the increase in liver size were disproportionately greater than the increase in total body mass improvement in hepatic function might be attributed to this rapid growth of the liver. From the work of Potter and Adair,[49] however, it appears that for fetuses weighing up to 4250 gm. the increase in liver size is directly proportional to increase in body weight. Thus, organ mass, as body weight, is not the determining factor in the progressive maturation of hepatic function as measured by the bromsulphalein test.

Parallel studies could not be performed on normal newborns in sufficient numbers to permit a direct comparison with the prematures. However, the results of the 45 minute retention test in the newborns up to 10 days of age, as obtained by Yudkin and Gellis,[4] show much the same distribution of values as do the prematures over the same period. A single BSP excretion test performed in a 3.2 kg. infant at 3 hours of age gave a curve indistinguishable from those of the prematures one day of age. Thus, it seems likely that prematures 2 to 3 weeks old would have demonstrably better hepatic function than full-term infants on the first day of life although they weigh considerably less. It is also likely that a study of the excretion curves of newborns of varying age would show the same improvement with age as do the prematures but possibly telescoped over a shorter period.

Summary and Conclusions

In normal adults, following a single intravenous injection of BSP, the logarithmic decline of plasma BSP levels is rectilinear. In patients with hepatic disease, the plotted values are curvilinear with flattening of the curve, or "saturation," occurring at high plasma BSP concentration. The use of the excretion curve provides a dynamic representation of the hepatic uptake of dye throughout the test, avoids the theoretic objections to the 45 minute test, and obviates the necessity for plasma volume determinations.

Thirty-five healthy prematures of varying age and weight were the subjects of a study of liver function by the bromsulphalein excretion test. As measured by the BSP excretion test, there is progressive maturation of liver function with age in prematures which does not necessarily correlate with weight. The excretion curves obtained in prematures 18 to 28 hours of age resemble those of older patients with severely impaired hepatic function. Clearance of dye in these subjects is slow throughout the test. With increasing age there is a gradual change in the pattern of the curves characterized by the appearance of the initial sharp slopes coincident with rapid dye removal. "Saturation," or flattening of the curves, persists until a later age and takes place at progressively lower plasma levels. This biphasic pattern is apparent in the prematures over 4 days of age. The normal adult pattern is not attained until about 6 to 8 weeks although the 45 minute retention values become normal at three weeks.

The gradual development of normal excretion curves in premature infants may be explained by the progressive maturation of the anatomic and physiologic factors involved in the mechanism of BSP clearance. The increasing size of the capillary network in the liver that occurs with advancing age in effect increases hepatic blood flow and exposes a greater volume of blood in the sinusoids to the activity of the liver. The appearance of the initial sharp slopes, representing rapid dye removal, probably results from this increasing vascularity and possibly from maturation of the hepatic uptake mechanism. The continuance of the biphasic character of the curves probably results from inability to excrete the dye efficiently into bile.

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SPANISH ABSTRACT

La Prueba de la Excrecion de la Bromosulfaleina (BSP) Como Una Medida de la Funcion Hepatica en los Niños Prematuros

En el adulto normal después de una inyección intravenosa única de bromosulfaleina, la disminución logarítimica de los niveles de esta substancia en el plasma es rectilínea. En enfermos con padecimientos hepáticos la representación gráfica de este dato es curvilínea con un aplanamiento, o "saturacion," que se presenta cuando la concentración de bromosulfaleina en el plasma es elevada. El uso de curvas de excreción provee una representación dinámica de la retención hepática del colorante en el transcurso de la prueba, evita las objeciones teóricas a la prueba de los 45 minutos y elimina la necesidad de determinaciones del volúmen del plasma.

Como una medida de la función hepática, en 35 prematuros sanos de diversas edades y pesos, se verificó la prueba de excreción a la bromosulfaleina. De acuerdo con este examen hay una maduración progresiva de la función hepática en prematuros relacionada con la edad pero no necesariamente con el peso. Las curvas de excreción obtenidas en prematuros de 18-28 hrs. de edad, semejan aquellas encontradas en pacientes mayores con insuficiencia hepática severa. En ellos la desaparición de colorantes es lenta durante toda la prueba. Con el aumento en edad hay un cambio gradual en el tipo de las curvas, caracterizado por la aparición de un descenso inicial rápido que coincide con la eliminación rápida del colorante. La "saturación," o aplanamiento de las curvas persiste hasta edades posteriores y tiene lugar con niveles del colorante en el plasma, cada vez menores. Este trazo difásico es aparente en prematuros de mas de 4 días de edad. El tipo normal de adulto no se alcanza sino hasta aproximadamente la 6a. u octava semana, aunque las cifras de retención a los 45 minutos lleguen a la normalidad a las 3 semanas.

El desarrollo gradual de curvas normales de excreción en prematuros, puede explicarse por la maduración progresiva de los factores anatómicos y fisiológicos relacionados en el mecanismo de la "clarificación" de la bromosulfaleina. Con la edad aumenta la red capilar del hígado, lo que incrementa la circulación de esta viscera que pone en contacto, en los sinusoides, con la función hepática, un mayor volumen de sangre.

La aparición del descenso inicial rápido, que representa una eliminación pronta del colorante, resulta de la poca habilidad para excretar en la bilis esta substancia.

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REPORT OF TWO YEARS' EXPERIENCE IN THE TRANSPORTATION OF PREMATURE INFANTS IN NEW YORK CITY

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IN NEW YORK CITY, there are now approximately 157,000 live births each year, of whom 12,813 or 8½% are prematurely born when birth weight is used as the criterion of prematurity. Of the approximate 13,000 premature infants born annually, 3,610 weigh less than 2,000 gm. at birth. Because of the considerably higher mortality rates of premature infants in the lower weight groups, it is considered wise to provide specialized pediatric and nursing care for them. With the already low infant mortality rates in the city (24.9 per 1,000 live births in 1950) special attempts to save lives of those born prematurely provide an effective way of further reducing the loss of infant life. Preventing premature labor is of course fundamental to the solution of the problem and is being attacked in various ways.

This paper, however, is chiefly concerned with the experience that has accumulated in the two year period (November 1, 1948—November 1, 1950) with a group of 1,209 prematurely born infants who were transferred from the place of birth (hospital or home) to a "premature center." The establishment of the transport service was but one part of an accelerated postwar program to reduce deaths associated with prematurity. The entire program is a voluntary one—in that physicians, hospitals and patients cooperate on a voluntary basis under the general guidance of an expert team of pediatricians, obstetricians and nurses who are fulltime or part-time employees of the Maternity and Newborn Division of the Department of Health.

The ambulance service is operated jointly by the New York City Departments of Health and Hospitals; the ambulance, its equipment, oxygen and drivers are supplied by the latter Department; the Health Department provides the nurses for the transport service, the clerical staff, and the medical and nursing administration and supervision of the service. Priority in transport is given to the following babies: (1) the smallest babies; (2) babies in the poorest condition; (3) babies born in the poorest hospitals; (4) babies born at home. Details of the planning and initiation of the transport service have already been published.[1]

Concomitantly with the establishment of the transport service, facilities for care of prematures were improved and expanded in six "premature centers" having a total capacity at present for 143 infants. Seven more "centers" are currently being planned or constructed with a capacity for 220 additional infants.

This report will describe some of the accomplishments and problems of a transport service during the early and intermediate stages of the development of a community pre-

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mature program. It will also portray certain patterns of medical practice as gleaned from the records of the premature infants transported.

Analysis of Premature Infants Transported

1. Infants Transferred and Their Hospital Mortality Following Transport

During the first two years of the Transport Service, a total of 1,209 infants were transferred, of whom 543 were transported in the first year and 666 in the second year. A total of 307 babies died in the hospital following transport, of whom 146 died in the first year and 161 in the second year, with over-all hospital mortality rates following transport of 26.9% and 24%, respectively. The hospital mortality rates in the various birth weight groups were improved in the second year of transport over the first year's transport series (table 1). One explanation for this improvement might be the fact that during the second year two new premature centers were opened and practice in existing centers was improved.

It is obviously difficult, if not impossible, to compare the hospital mortality per cent of the two years' transport series with the experience of all premature infants born alive in the City during a year's period. The 1948 city-wide premature statistics are presented however for purposes of over-all comparison.

It is noted that in both years' transport series, approximately 85% of the infants transferred weighed less than 2,000 gm. at birth. In other words, as was the plan, emphasis has been given in placing the smallest infants in the premature centers. Usually the large premature infants transferred have been of two main types:

(a) Premature infants born at home and unable to be cared for there due to unsuitable home conditions.

(b) Hospital-born premature infants in poor condition at the time of transfer.

2. "Candidates For Transport" Who Were Transferred

In evaluating the effectiveness of a community program, it is essential to know the

TABLE 1

Birth Weight Distribution and Hospital Mortality of Premature Infants Transported in First and Second Years of Premature Transport Service, and Birth Weight Distribution of All Premature Infants Born Alive in New York City in 1948 and Mortality in First Year of Life

Wt. Group	No. Infants Transported		No. Premature Infants Born Alive in New York City in 1948	Hospital Mortality % of Premature Infants Transported		Mortality % in First Month of Life All Premature Infants Born Alive in 1948 in New York City
	11/1/48–11/1/49	11/1/49–11/1/50		11/1/48–11/1/49	11/1/49–11/1/40	
Under 1000 gm.	93	101	563	72.0%	71%	86.1
1000–1499 gm.	140	187	816	26.4%	23%	50.0
1500–1999 gm.	229	272	2,231	13.1%	10%	15.3
2000–2500 gm.	78	84	9,203	17.9%	7%	3.1
Over 2500 gm.	3	21		33.3%	52%	
Unknown	—	1		—	100%	
Totals	543	666	12,183	26.9%	24%	12.2

TABLE 2

BIRTH WEIGHT DISTRIBUTION OF PREMATURE INFANTS WHO WERE CANDIDATES FOR TRANSFER AND PERCENTAGE TRANSFERRED

Wt. Group	1948 New York City Premature Statistics			Transport Experience		% of "Candidates"* Who Were Transferred	
	No. Born	No. Born in Premature Centers	No. Born in Other Hospitals and at Home*	No. Transferred			
				11/1/48–11/1/49	11/1/49–11/1/50	11/1/48–11/1/49	11/1/49–11/1/50
Under 1000 gm.	563	212	351	93	101	26.5%	28.8%
1000–1499 gm.	816	308	508	140	187	27.5%	36.8%
1500–1999 gm.	2,231	839	1,392	229	272	16.5%	19.6%
2000–2500 gm.	9.203	3,759	5,444	78	84	1.4%	1.5%
Over 2500 gm.	—	—	—	3	21		
Unknown	—	—	—	—	1		
Totals	12,813	4,819	7,994	543	666	6.8%	8.3%

* "Candidates for Transfer."

volume of coverage of the community population for whom the program is intended. Table 2 demonstrates that only 8.3% of candidates for transfer were transferred. In individual weight groups the extent of coverage was as high as 37%. Furthermore, the extent of coverage increased in all weight groups in the second year as compared with the first year of the Transport Service.

3. Requests For Transport Which Could Not Be Met

The question is frequently raised by pediatricians concerning the fate of premature infants who could not be transferred due to the lack of a vacancy in a "premature center" even though request for transport was made. During the first two years of the Premature Transport Service, requests were received to transfer an additional 368 infants who were not transported because of the lack of a bed in a "center." Thirty-nine per cent died at the place of birth. The hospital mortality rates of this group in the three lowest individual birth weight groups are considerably higher than the rates for the transport series, and in some birthweight groups even higher than the 1948 city-wide premature statistics (table 3). In general, these facts should be correlated with the following priorities established for the Transport Service: (1) infants in the lowest birth weight groups; (2) infants in poor condition; (3) infants born in the most substandard hospitals; (4) infants born at home. In other words, no attempt was made to select the "best babies" for transport.

4. Cooperation of Hospitals

In the first two years of the Transport Service, 101 hospitals cooperated in the premature program, of whom 5 were nonmaternity hospitals and 96 were maternity hospitals. All the 13 municipal hospitals, all but 1 of the 30 proprietary hospitals, and all but 10 of the 64 voluntary hospitals cooperated. Thus, of the 107 maternity hospitals, 96 or 90% cooperated; of these 96 maternity hospitals, 16 received infants from the outside and 80 transferred premature infants to the 16 hospitals. This degree of cooperation

TABLE 3

REQUESTS FOR TRANSPORT WHICH COULD NOT BE MET 11/1/48 TO 11/1/50 AND FATE OF THIS GROUP

Wt. Group	Total Not Transferred	Survived at Place of Birth	Died at Place of Birth	Disposition Unknown	Hospital Mortality Per Cent
Under 1000 gm.	56	3	52	1	93%
1000–1499 gm.	58	15	41	2	71%
1500–1999 gm.	147	96	41	10	28%
2000–2500 gm.	85	73	3	9	4%
Over 2500 gm.	4	1	0	3	0
Birth Wt. Unknown	18	3	6	9	33%
Totals	368	191	143	34	39%

in the early and intermediate phases of the program is highly gratifying, and shows the degree of realization by hospital and medical personnel that the smaller premature infant deserves the best care that a community has available.

5. Category of Patients Transferred

Of the 1,209 infants transferred in the first two years, 890 (73.6%) were born on the private service and 319 (26.4%) were born on the general service. The fact that 74% of the babies transferred were delivered by private physicians shows the extent of cooperation and support of the community premature program by practicing physicians. It should be pointed out that in the planning and initiation of this Service, considerable time was taken to explain the various aspects of the program to organized medical, hospital, and nursing groups and to individual practicing physicians. This step is essential if a community program is to be used to its fullest advantage and if there are understanding and cooperation of all groups concerned.

6. Time After Birth When Transfer Was Accomplished

The intent has been to transfer all premature infants needing transfer as soon after birth as possible. Of the 1,209 infants transported, 551 (45.5%) were transferred in the first day of life, 260 (21.5%) in the second day, 198 (16.3%) in the rest of the first week, and 199 (16.5%) after the first week of life. Thus, the objective of transferring all infants needing transfer immediately after birth was not approached for several reasons: (1) lack of vacancies in centers; (2) the tendency of some hospitals to keep the infant for financial reasons at the place of birth until the mother was discharged. The availability of more beds in centers and further education of hospital personnel are necessary before this objective can be fully achieved.

A question frequently asked is whether it is desirable to have such a policy of immediate transfer after birth, or whether it would be better to wait until the second or even third day of life. The data in table 4 are presented with this question in mind. As would be expected it would appear that the older the infant at transport, the better chance he has for survival. This conclusion may not be justified, however, since the policy has been to transfer even infants in poor condition immediately after birth at the request of desperately anxious physicians, hospitals and parents. This policy obviously has a profound influence on the data presented in table 4.

TABLE 4

EFFECT OF AGE AT TRANSFER UPON HOSPITAL MORTALITY—
FIRST 2 YEARS OF TRANSPORT SERVICE
Age at Transfer*

Wt. Groups	Under 1 Day			2nd Day			3rd Day and Over		
	Transferred	Died	Mort. %	Transferred	Died	Mort. %	Transferred	Died	Mort. %
Under 1000 gm.*	153	116	75.8%	28	18	64.2%	12	4	33%
1000–1499 gm.	172	51	29.5%	70	18	25.7%	85	10	11.7%
1500–1999 gm.	167	31	18.5%	125	11	8.8%	209	15	7.1%
2000–2500 gm.	51	9	17.6%	35	6	17.1%	76	4	5.2%
Over 2500 gm	7	2	30%	2	2	100%	15	8	53.3%
Unknown	1	1	100%	—	—		—	—	—
Totals	551	210	38%	260	55	21.1%	397	41	10.3%

* One additional infant 1,000 gm. was transferred, age at transfer unknown.

One might conjecture from a long range point of view that, if the level of immediate care at the place of birth is of a high caliber, it would be desirous to delay transfer for a day or so. This would mean that each maternity hospital would have to have at least one nurse on duty at all times who has had special training in the care of the premature, as well as special facilities (heat and oxygen) and good emergency standing orders and service for such immediate care. Such a situation does not obtain in all maternity hospitals in New York City at present nor is there any way now to provide adequately for the small premature born at home who still would need to be transferred early.

7. Length of Time During Transport

During the first two years of the Transport Service, the special ambulance made 1,134 trips lasting a total of 124,725 minutes, or an average of 110 minutes per trip from the time the ambulance left the Transport Office until it returned. The time the infants were actually in transit in these 1,134 trips was 30,186 minutes or an average of 27 minutes for each infant or set of infants in transport. It took the Transport Service a period of approximately five months after its initiation to become a well organized program and to learn geographic locations and travel routes to hospitals; this fact is reflected in the longer average time in transport in the first five months of the service, and the stabilized duration of trips thereafter.

8. Average Length of Stay in Centers

The average length of stay in the hospital following transport of this group of 1,209 infants was 33 days, which compares favorably with other similar reports.[2,3]

Since July 1, 1950, the New York City Health Department has been paying for the hospital care of premature infants in approved "premature centers" at a ceiling rate of $12.00 per day. During the first 12 months of the payment program, a total of $285,505.75 has been expended for the hospital care of 915 premature infants, or a cost of $312.03 per infant, or an average length of stay of 26 days per infant in the centers. Families are asked to pay all or whatever they can toward the cost of care for these babies. The hospital determines the families which are eligible for the service on the basis of criteria agreed upon previously by the Department of Health and the hospitals. Actually only a small per cent have been able to pay much of the bill so that excluding those families who meet full cost the Health Department has paid for 97.3% of the hospital bill, the family or other source 2.7%.

9. Cost of the Transport Service

In planning for a Transport Service many questions arise the answers to which at present have very little supporting data. Is it better for the administrative agency to provide the ambulance service directly, or to purchase ambulance service from a hospital or commercial ambulance company? Who should staff the ambulance service—nurses, and if so after what kinds of training; firemen; or policemen? After careful review of the situation, it was decided that the two City Departments (Health and Hospitals) would provide and operate the ambulance service, and that the service would be staffed at all times by a nurse who has had special training in the care of the premature infant. So far,

TABLE 5

COST OF OPERATION OF TRANSPORT SERVICE, NOV. 1, 1948–NOV. 1, 1950

Item	Amount	
	Per Year	For 2 Yr. Period
Personnel		
Ambulance Drivers 5 @ $2,890	$14,450.00	$28,900.00
Nurses 5 @ $2,400	12,000.00	24,000.00
Clerk	1,860.00	3,720.00
Equipment		
Oxygen		$ 627.60
*Ambulance		486.00
Construction of ambulance		500.00
Portable incubators (5)		250.00
†Other equipment (supplies, etc.)		300.00
Total		$58,783.60

* Original cost of ambulance was $2,434 in 1940. Depreciation of 10% allowed per yr. for 10 yr.
† Original cost of total equipment was $1,500. Depreciation of 10% allowed per yr. for 10 yr.

these decisions have proved to be justified for many reasons: (1) there is considerable belief that it is better for the infant, i.e., the amount of heat and oxygen are carefully supplied, and emergency measures such as suction and stimulants are always available during each trip; (2) the ambulance service can be carefully controlled and supervised; (3) the ambulance service can be closely integrated with the basic maternity and newborn program in many ways.

In the early stages of a program, until enough "premature centers" are developed, the provision of an ambulance service is undoubtedly more costly than the purchase of service within a community. It cost $58,783.60 to operate the service for the transport of 1,209 infants over a two year period, an average of $48.62 per infant (table 5) for the two year period; the cost was $54.13 during the first year and $44.13 during the second year. The volume of transport (1,209 infants over a two year period) represents an average of 1.7 transports per day. The volume of transports per day could easily be doubled and probably tripled, thus reducing the cost per trip by one-half or two-thirds, as the program develops.

Indices of Patterns of Medical Care

In planning the records for the Premature Transport Service, a record form of the infant was devised so that the receiving hospital or "premature center" would have pertinent data on the mother's antepartum and intrapartum course and on the course of the infant from birth to time of transport. Some of the pertinent data were studied in order to glean some picture of medical care in an urban area.

A total of 59 mothers (5%) had received no antepartum care. Seventy-five women (6%) had no serologic test for syphilis during their pregnancy; there were no data on the performancy of a serologic test for 112 women (9%). Eighty-eight women (7%) had a serologic test, the results of which were unknown; this group is usually composed of women having their test done at the time of labor and delivery. Only eight women had a positive serologic test for syphilis.

Rh determination was performed during the pregnancy of 653 women (54%); the frequency of Rh testing rose from 45% during the first year of transport to 60% during the second year.

Although the value of vitamin K in the prevention of hemorrhagic phenomena in premature infants is still being debated, it has been widely recommended by obstetric groups for patients in premature labor. If not given to patients in labor, it has been recommended for use in the premature infant immediately after birth.[4,5] Only 14 patients in labor (1%) received vitamin K. Six hundred and nine premature infants (50%) received vitamin K; the percentage of infants increased from 37% in the first year of transport to 62% in the second year.

Some obstetric authorities have recommended that women in premature labor receive no analgesia, so that asphyxia neonatorum at least from this etiology may be prevented.[6–8] A total of 235 women (19%) received some analgesic agent, demerol alone or in combination being the most frequently used. Morphine was used in 25 women (2%) in spite of its known markedly depressant effects on the fetus.

It is well known that there is some degree of danger in the too rapid delivery of a premature infant, as well as danger in prolonged labor.[9] In this series, 19% of the women had a rapid or precipitate delivery (3 hours of labor or less). Approximately 2½% of the women were in labor more than 24 hours. In 22% of the women there were no data on duration of labor.

In the delivery of a premature infant, many obstetric authorities have recommended the use of prophylactic outlet forceps.[6,10] Of the 923 vertex presentations, only 143 (15%) were delivered by forceps.

It has been recommended that a general inhalation anesthesia not be used for women who are expected to deliver a premature infant.[11] In this series, 528 women received some type of anesthetic, of whom 418 (79%) received a general inhalation type of anesthesia.

A total of 422 women (35%) had a known complication of pregnancy; the commonest complications were toxemia, placenta praevia, abruptio placentae, and premature rupture of the membranes, which occurred in 71% of the women who developed complications.

In this group, 558 women were primiparae and 751 women were multiparae. In this group of multiparae, there were delivered 188 previous premature infants and 184 previous fetal deaths. In other words, one multiparous woman out of every four had delivered a previous premature infant, and one out of every four had delivered a previous stillborn

infant. These facts demonstrate the importance and potentialities of preconceptional care.

Place of Birth of Infants Transported

In the first two years of the Transport Service, 1,073 infants (89%) were born in hospitals and 136 infants (11%) were born at home. Some interesting facts emerge in a special analysis of the home-born group: the hospital mortality following transport was considerably higher in the three lowest birth weight groups (under 2,000 gm.); a higher percentage of infants were transported in the first day of life; a higher percentage of the mothers were nonprivate patients; a higher percentage of the mothers had no antepartum care, no serologic test, no Rh determination and no vitamin K; and a higher percentage of women delivered at home had precipitate deliveries. The greater vulnerability of the home-delivered group is apparent.

Discussion

The importance of a basic community maternity and newborn program[12] upon which a community premature program is superimposed cannot be too greatly emphasized. For example, without the basic maternity and newborn program, it is doubtful if the following could have been accomplished as rapidly: (1) the construction of new "premature centers" and the training of personnel; (2) the cooperation of 90% of a community's hospitals in the first two years of the Transport Service; (3) the extensive use of the Transport Service by private physicians. Furthermore, only knowledge of hospital conditions at the place of birth, through the basic maternity and newborn program, has enabled the administrators of the program to use the place of birth as one of the factors in determination of priority of transport. Obviously, too, a community-wide maternity and newborn program is essential in any preventive plan designed to reduce the incidence of premature birth.

This report of the first two years of a Premature Transport Service depicts the results of a program which has relied completely upon the voluntary interest and cooperation of hospitals and physicians. This interest and cooperation have been most gratifying. When the city-wide premature program is fully developed, it is anticipated that there will be a need of 18 to 20 premature centers located strategically throughout the City. If all the roughly 3,500-4,000 premature infants weighing less than 2,000 gm. born each year in the City are to receive the high quality of pediatric and nursing care usually only provided in premature centers and if these infants are to be transferred reasonably early after birth, immediate reporting of premature birth must be required. It is anticipated that this requirement will be a reality in the future when there is a sufficient number of centers.

Most authorities are of the opinion that, as well as providing better pediatric and nursing care for the prematurely born infant, there must be concomitant improvement in the level of obstetric practice in the antepartum and intrapartum periods, if there is to be a significant saving of infants' lives.[13] There is evidence in this report that not all known preventive and precautionary measures are being taken at present, as witnessed by the following findings: (1) Not all women in this series received at least some degree of antepartum care. (2) Not all women had a serologic test for syphilis, and Rh test. (3) Few women in premature labor received vitamin K. (4) Some women in premature labor received an analgesic agent, including morphine. (5) Some women received a general inhalation type of anesthesia during delivery. (6) Not all women with vertex presentation were delivered by prophylactic low forceps. Thus, there is need for con-

siderable professional and public education so that there may be better understanding of the important steps to be taken if the loss of life associated with premature delivery is to be cut down. Methods to "glamorize" better antepartum and intrapartum care to the same extent as ambulances, incubators and premature centers must be found.

The fact that one out of every two multiparous women in this series had previously delivered a premature infant or a fetal death perhaps provides another approach to this problem of loss of life and pregnancy wastage. Logical steps would be to provide facilities in which studies could be made of the possible factors contributing to prematurity and fetal death in such cases and to be more alert to the possibility of and prevention of premature labor in those pregnancies which have previously ended in premature labor. Out of such studies a more definitive type of preconceptional care will certainly emerge.

Evidence has already seen that the home in the urban situation currently found in New York City is a less safe place for delivery than the hospital, from the viewpoint of maternal mortality.[14] In this report, there is evidence that this lesser degree of safety in home delivery under the conditions found today in New York City is applicable to the premature infant.

Summary

This report has presented some facts about premature infants based on a two year experience in the transportation of 1,209 small prematurely born infants to special "premature centers" in New York City. The data point the way for further developments in a program of care for the premature infant and in the prevention of premature labor. The importance of the parallel development of a sound maternity program and a special program to care for the prematurely born infant is emphasized.

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SPANISH ABSTRACT

Dos Años de Experiencia en el Transporte de Prematuros en la Ciudad de New York

Este artículo describe la experiencia obtenida en la ciudad de Nueva York, al transportar 1209 niños prematuros a centros especializados para su atención, en un lapso que abarcó desde el lo. de noviembre de 1948 hasta el 1° de noviembre de 1950. Los datos importantes recogidos fueron: (1) las tres cuartas partes de los niños sobrevivieron en los hospitales después de su transporte; (2) únicamente 8.3% de todos los candidatos fueron transportados; en los grupos individuales, de acuerdo con el peso, hasta un 37% de ellos fueron aceptados; (3) 90% de los hospitales con servicios de maternidad y de recién nacidos participaron en el programa; (4) 74% de los niños nacieron en los servicios privados de hospitales; (5) 46% fueron transportados en el primer día de vida; (6) se utilizó un promedio de 27 minutos para el transporte; (7) la permanencia en los centros especializados fué de 33 días; (8) el costo promedio por niño en estos sitios fué de 312.03 dls.; (9) el costo promedio por viaje de ambulancia fué de 48.62 dls. por niño. En la parte final del trabajo se analiza la atención médica materna tomándola como un reflejo del servicio médico actual en la ciudad y haciendo notar la necesidad de mejorar antes y durante el parto los cuidados que recibe la madre.

125 Worth Street

DUPLICATIONS OF THE ALIMENTARY TRACT

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DUPLICATIONS are spherical or tubular structures which possess a well developed smooth muscle layer and are lined with a mucous membrane; they are found at any level from tongue to anus and usually are intimately attached to some portion of the alimentary tube. From 1928 through 1950, 67 patients with a duplication of some portion of the alimentary tract have been seen at Children's Hospital in Boston. Only 18 cases were detected in this institution prior to 1940; since that time 49 patients have been found to have this congenital anomaly (one male infant had two separate lesions making a total of 68 duplications). Twenty-three of these cases have been reported previously[1-5]; for the sake of completeness, all of them are included in the present study.

TERMINOLOGY

The term "duplication of the alimentary tract" is preferred by the authors because it simplifies the classification of these malformations which are found in such diverse locations and which vary so greatly in shape and size. In reviewing the literature one finds these anomalies called "enterogenous cysts," "giant diverticula," "ileum duplex," "thoracic cysts of enteric origin," "bronchogenic cysts," "unusual Meckel's diverticula," etc. Such appellations have been used, believing that each was a separate entity, depending upon its location and its physical form. It is now the authors' belief that all duplications have a similar origin, regardless of their location.

The term "bronchogenic cyst" was probably suggested when pseudostratified columnar cells were found lining some of the thoracic duplications. However, such an epithelium could persist from cells which line the primitive gut in 9 to 11 week embryos. Referring to this lesion as "bronchogenic," therefore, seems unjustified; this is especially true when one recalls that other bowel structures such as smooth muscle and serosa constitute large portions of the cyst walls. A term such as "enterogenous cyst" implies close association with the intestinal tract, but it could hardly include those lesions which lie free on their own mesentery and the one (Case 14, Table A) attached to the diaphragm. "Giant diverticulum" suggests a connection with the bowel lumen, but would be unsuitable for the larger group in which no such communication exists. "Ileum duplex" and "thoracic cysts of enteric origin" describe only the lesions located in those specific regions. "Unusual Meckel's diverticulum" denotes embryologic derivation from a Vitelline duct; the discovery of a duplication and a Meckel's diverticulum in the same patient as reported by Edwards[6] disproves this theory of origin since there is only one Vitelline duct. Because of such specific objections to the more limited terms, it seems preferable to classify all these anomalies under the all-inclusive name of "duplications of the alimentary tract."

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TABLE A

DATA FROM 68 DUPLICATIONS OF ALIMENTARY TRACT

Case	Age	Location of Cyst; Relevant Figures	Size of Duplication; Type of Mucous Membrane	Treatment	Result
1*	—	Base of tongue	1 cm. in diameter. Colonic	Excision	Recovered
2*	7 wk.	Right pleural cavity (middle)	5 cm. in diameter. Gastric	Excision	Recovered
3*	2 yr.	Right pleural cavity	10×6×5 cm. Gastric	Excision	Recovered
4*	7 mo.	Right pleural cavity	8×5×4 cm. Gastric	Multiple marsupializations	Died
5	22 mo.	Para-esophageal, left (lower) (Fig. 5)	8×5×4 cm. Pseudo columnar	Excision	Recovered
6*	3 wk.	Lower esophagus, left	1.5 cm. in diameter. Gastric	Marsupialization and curettage	Recovered
7	6 wk.	Lower esophagus, right	5 cm. in diameter.	Marsupialization and curettage	Recovered
8	20 mo.	Esophagus, right (Fig. 6)	3×2×0.5 cm. Pseudo columnar	Excision	Recovered
9	6 wk.	Esophageal, with fistula to left upper lobe	2.5×2 cm. Gastric	Excision of duplication and left upper lobectomy	Recovered
10	5½ yr.	Lower esophagus, right	12×8×8 cm. Pseudo columnar	Excision	Recovered
11*	1 yr.	Midesophagus, right	.... Gastric	Marsupialization	Recovered
12	5 wk.	Upper esophagus, right	5.5×3.5×3 cm. Small intestine	Excision	Recovered
13	1 mo.	Lower esophagus, left (Fig. 4)	6×2.5 cm. Colonic	No therapy. Found at autopsy	Same patient as #28
14	3½ yr.	Right pleural cavity (attached to diaphragm)	5×6 cm.	Excision	Recovered
15*	4½ yr.	From duodenum, entering R chest	20×2.5 cm. Gastric	Excision of supradiaphragmatic portion	Recovered
16*	4 mo.	From jejunum, entering R chest	27×2.5 cm. Small intestinal	1 stage complete resection and anastomosis of jejunum	Recovered
17*	3½ mo.	From jejunum, entering R chest and into L chest	30×2 cm. Colon, ileum, pseudo columnar	Multiple stage removal of supra-diaphragmatic portions	Recovered
18*	7 yr.	Along stomach	Large as stomach. Necrotic mucosa	Partial excision and marsupialization	Recovered
19	3 days	Greater curvature of stomach	4 cm. in diameter. Gastric	Excision duplication and gastrostomy	Died
20*	5 wk.	Duodenum (Fig. 8)	4.5×3.5×3.5 cm. Duodenal	Resection; gastrojejunostomy	Recovered
21	8½ yr.	Duodenum (Fig. 7)	3×4 cm. Small intestinal	Window cut into duodenum	Recovered
22	1½ yr.	Duodenum	5 cm. in diameter.	Window cut into duodenum	Recovered
23	2 yr.	R side of duodenum	2.5×2.5 cm. Gastric	Excision	Recovered
24*	6 mo.	Jejunum	22×6×6 cm. Gastric	Mikulicz resection (perforated)	Died
25*	2 wk.	Jejunum	4 cm. in diameter. Jejunal	Resection and anastomosis	Recovered
26	3 days	Jejunum	4×3×3 cm. Small intestinal	Resection and anastomosis	Died
27	13 yr.	Jejunum	30×5–10 cm. Gastric	Resection and anastomosis	Recovered
28	1 mo.	Jejunum and ileum (Fig. 10)	65 cm. long. Small intestine	(Perforated) Resection and anastomosis	Died

TABLE A—(*continued*)

Case	Age	Locagion of Cyst; Relevant Figures	Size of Duplication; Type of Mucous Membrane	Treatment	Result
29	1 day	Upper ileum	23×9 cm. Pyloric	Resection and anastomosis†	Recovered
30	10½ mo.	High ileum	1.5×1.5 cm. Ileal	Reduction intussusception. Resection of duplication	Recovered
31	3 yr.	Upper ileum	6 cm. in diameter. Small intestine	Excision†	Recovered
32	4 mo.	Detached from high ileum	52 cm. long. Gastric	Anastomosis distal end duplication to ileum†	Recovered
33*	3 mo.	Ileum	7×4×4 cm. Gastric	None	Died
34	1 day	Ileum	5.5×4.5×2.5 cm. Necrotic	Resection and anastomosis	Recovered
35	9 days	Ileum	3.5×2 cm. Small intestine	Resection and anastomosis	Recovered
36*	6 yr.	Ileum	3 cm. diameter Ileal	Resection and anastomosis	Recovered
37*	2 yr.	Ileum (Fig. 9)	38 cm.×2 cm. Gastric	Resection and anastomosis	Died
38	4 mo.	Ileum	1×1 cm. Gastric	Resection and anastomosis	Recovered
39	9 days	Midileum	30×5 cm. Pyloric and colonic	Resection and Mikulicz ileostomy	Recovered
40	1 day	Low ileum	44×1 cm. Small intestine	Excision	Died
41*	12 days	Terminal ileum	1.5 cm. diameter. Ileal	Resection and anastomosis	Recovered
42*	2 mo.	Terminal ileum	2 cm. diameter. Ileal	Resection and anastomosis	Recovered
43	2 yr.	Terminal ileum (Fig. 11)	3.8×3.2 cm. Gastric	Resection and anastomosis	Recovered
44	10 days	Lower ileum	3.5×2 cm. Pyloric	Resection and Mikulicz ilecstomy	Recovered
45	18 mo.	Terminal ileum	3×2×1.6 cm. Gastric, ileal, colonic	Excision	Recovered
46	3 wk.	Terminal ileum	3×1.5 cm. Ileal	No therapy. Found at autopsy	Died
47*	19 mo.	Detached from terminal ileum	15.5×4×5 cm. Columnar	Excision	Recovered
48	3 mo.	Ileocecal junction (Fig. 13)	3×2×2 cm. Small intestine	Resection and ileocolostomy	Recovered
49	3 days	Ileocecal junction	3 cm. diameter. Small intestine	Mikulicz resection gangrenous ileum and cecum†	Died
50	1 wk.	Ileocecal junction	5.5×3 cm. Small intestine	Resection and ileocolostomy	Recovered
51	10 mo.	Ileocecal junction (Fig. 13)	5×4×3.5 cm. (Quadruplication)	Resection and Mikulicz ileocolostomy	Recovered
52	10 mo.	Ileocecal junction	2.5 cm. diameter. Low cuboidal	Resection and Mikulicz ileocolostomy	Recovered
53	13 mo.	Ileocecal junction	5×4 cm. Ileal	Reduction intussusception. Resection and ileocolostomy	Recovered
54	3½ yr.	Ileocecal junction	3×3.5 cm. Small intestinal	Resection and ileocolostomy	Recovered
55	8 mo.	Ileocecal junction	6×3.5×3.5 cm. Columnar epithelium	Resection and ileocolostomy	Recovered
56	5 days	Detached from transverse colon	3.5×2.5 cm.	Excision	Recovered
57	8 mo.	Cecum	2 cm. diameter. Colonic	Reduction intussusception. Resection and ileocolostomy	Recovered

TABLE A—(*continued*)

Case	Age	Location of Cyst; Relevant Figures	Size of Duplication; Type of Mucous Membrane	Treatment	Result
58*	3 mo.	Cecum	4 cm. diameter. Colonic	Reduction intussusception. Resection and anastomosis	Died
59	3 wk.	Cecum	5 cm. diameter. Colonic	Resection and ileocolostomy	Recovered
60*	2 wk.	Sigmoid	12×10×8 cm. Ileal and colonic	No therapy. Found at autopsy	Died
61	2 yr.	Sigmoid	2.5×0.6 cm. Large intestinal	Resection and anastomosis	Recovered
62*	6 mo.	Posterior to rectum	5×2.5×2.5 cm. Mixed	Excision. Rectum repaired	Recovered
63	1 yr.	Posterior to rectum (Fig. 14)	4 cm. diameter. Mucosa ulcerated	Excision	Recovered
64	2 mo.	Posterior to rectum	2.4 cm. diameter. Intestinal	Excision	Recovered
65	14 days	Double lumen rectum. (Imperforate anus) (Fig. 15D)	5×0.5 cm. Rectal	No therapy. Found at autopsy	Died
66	4 mo.	Double lumen terminal ileum, appendix, transverse and descending colon (situs transversus) (Figs. 15A and 16)	Terminal ileum to rectum Colonic	Closure recto-urethral fistula. Resection descending colon. 2 rectal lumina made into 1. (3 operations)	Recovered
67	6 wk.	Double lumen, descending colon to anus (Fig. 15B and 17)	15×5 cm. Colonic	Closure recto-urethral fistula. Resection descending colon. 2 rectal lumina made into 1. (3 operations)	Recovered
68*	12 yr.	Double lumen, colon and rectum (Fig. 15C)	18×2 cm.	Accessory anal opening closed. 2 rectal lumina made into 1.	Recovered

* Cases previously reported from this hospital.
† Also had Ladd procedure for malrotation.

EMBRYOLOGY

Many theories have been advanced to explain the origin of duplications. Edwards[6] believed that they resulted from an attempt at formation of a twin which occurred at such a late stage the effect was limited to a segment of bowel. Reversion to earlier phylogenetic forms has been considered, following observations that double ceca occur in fowls.[2] Some observers maintain that duplications occur as a result of diverticula formation; Lewis and Thyng[7] found intestinal outpouchings in a majority of rabbit and pig embryos, as well as in several human specimens, of 4 to 8 weeks of age (10 to 30 mm.). However, these evaginations occurred most often on the antimesenteric side, whereas duplications usually are found along the mesenteric border. The diverticula described by Lewis and Thyng normally disappear but occasionally will persist and, if restricted in expansion by the muscle layer, will remain submucosal in location; more often, they perforate the muscle layers along paths of blood vessels and continue their expansion by pushing the serosa outward. The process may become arrested here or it may continue so that a free cyst is formed. Thus it is evident that the diverticula under discussion could form a simple cyst having only mucosa and serosa, but, according to Bremer,[8] it is inconceivable that one could give rise to a duplication which retains all the elements of a normal bowel wall.

Bremer[8] proposes the most plausible theory for the origin of duplications by recalling that in the embryo of about six weeks the lumen of portions of the intestinal tract may become completely occluded by the rapid proliferation of epithelial cells. Vacuoles begin

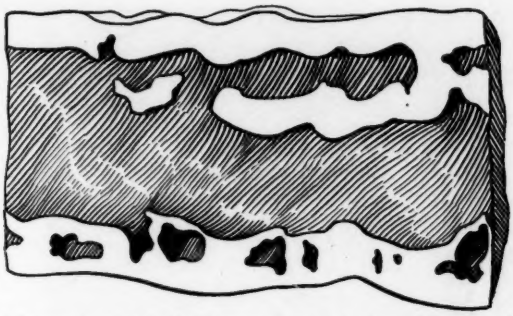

FIG. 1. Sketch of Johnson's model of esophagus at 7th wk. Above main lumen is confluent chain of vacuoles with 2 orifices. Below main lumen individual vacuoles are seen in thickened epithelium; these have not yet coalesced.

to appear in this cell mass as the intestinal tract grows in length. After these spaces form, they coalesce and usually arrange themselves in longitudinal rows parallel to the long axis of the bowel. Eventually, all such isolated vacuoles, of whatever size or shape, join one another to produce the normal lumen of the intestine. A drawing made from the original model by Johnson[9] (Fig. 1) indicates that persistence of one of these hollow spaces can lead to formation of a duplication. Also it is evident how possibly one or more connections (or even none) might occur between the bowel and its duplicate. Reference to figure 2 reveals diagrammatically how a duplication develops all muscle layers of the intestinal tract and may possess a common wall with the bowel or may hang free on its own mesentery. It also becomes apparent that a duplication might assume a wide variety of shapes and sizes and may be located anywhere along the alimentary tract.

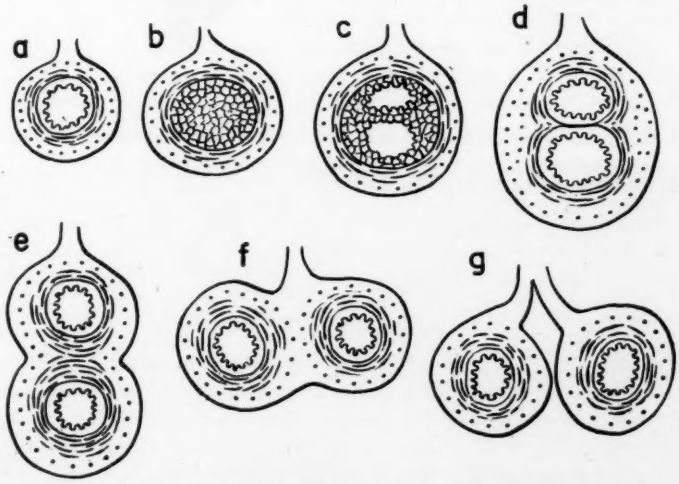

FIG. 2. Diagram of development of duplication: (a) early stage of alimentary tube; (b) solid stage; (c) 2 vacuoles in cell mass; (d) 2 epithelial lumina with conjoined basement membranes; (e) conjoined circular muscle layers between hollow structures; (f) same in horizontal position which can progress to (g) free duplicate tubes, each with complete intestinal wall and separate mesentery. (Redrawn from Bremer, J. L., Arch. Path. **38**:132, 1944.)

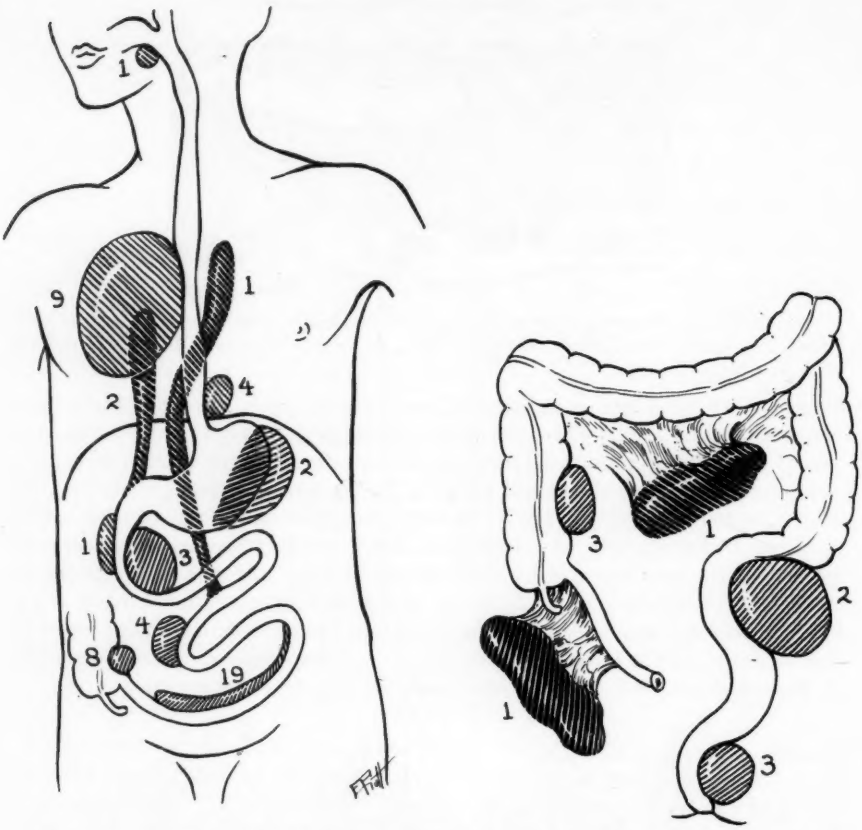

FIG. 3. Sketch illustrating distributions and general shapes of 64 duplications of alimentary tract. Figure beside each lesion indicates number of duplications found at that general site. (Four cases of double-lumen colon are sketched in Fig. 15.)

It is difficult to explain the origin of a triplication or a quadruplication by any theory except persistence of these vacuoles; a photograph (Fig. 13) of the specimen removed from Patient 51 illustrates these unusual findings.

PATHOLOGY

The most notable features of duplications are (1) a microscopic structure bearing striking resemblance to normal bowel, having mucosa, always one or several muscle layers, and often a well defined serosa; (2) each is lined with a mucosa similar to some portion of the alimentary tract (unless ulceration or necrosis has occurred); (3) those lesions which are contiguous with some portion of the intestinal tract share a common wall in which interlacing muscles are found.

Locations: The sites where the lesions were found in this series of patients are indicated in figures 3 and 15 and can be summarized as follows: base of tongue in one; arising within the thorax in 13; originating below the diaphragm but projecting into the thorax

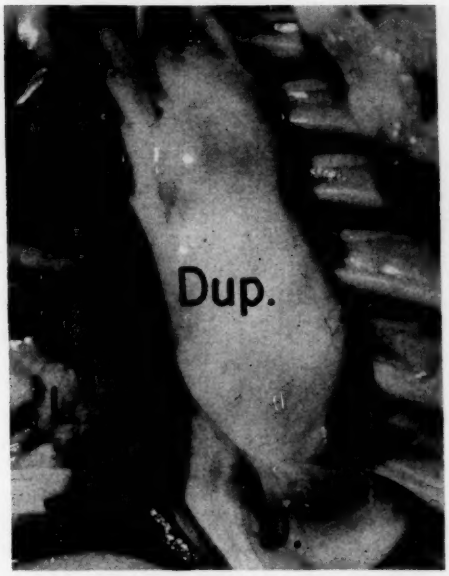

FIG. 4. Photograph of L pleural cavity taken at postmortem examination. Patient succumbed following resection of small bowel duplication 65 cm. in length, which had perforated, causing peritonitis. Esophageal duplication was incidental finding and had not produced symptoms. Note its posterior location as lung is held forward. D., L diaphragm. Dup., duplication. L., L lung.

in three; stomach in two; duodenum in four; jejunum in four; ileum in 20; ileo-cecal area in eight; on mesentery from transverse colon in one; cecum in three; sigmoid colon in two; posterior to the rectum in three; and double-barrelled lesions of the colon or rectum in four. Forty per cent of the lesions have been found along some part of the ileum. Excepting one, all lesions attached to the small intestine were found along its mesenteric border. Of the para-esophageal duplications, nine were located on the right side and four

FIG. 5. Left: AP RG of large, L esophageal duplication. Heart is displaced to patient's right, and barium-filled esophagus has indentation on its L side. Right: Lateral view of patient showing displacement of trachea anteriorly by mass (outlined by arrows) which lies close to spine.

FIG. 6. Left: RG from child with small, right, esophageal duplication (outlined by arrows). Right: Same patient following barium swallow, showing filling defect produced by para-esophageal mass.

on the left. Multiple duplications were found in only one patient (Specimens 13 and 28, Table A), who was operated upon for a duplication of the ileum and at postmortem examination was found to have also an esophageal lesion (Fig. 4).

Variations in Shape: Duplications assume various shapes; however, most of them will fall into one of the four following groups: (1) a tubular structure which branches out from the intestine and extends for some distance between the mesenteric leaves (Fig. 9) or proceeds into the thoracic cavity; (2) a double-barrelled structure, communicating with the intestinal lumen at one or both ends (Fig. 10); (3) a cystic structure, lying free in the peritoneal cavity, attached only by a thin mesenteric stalk (this is rare); and (4)

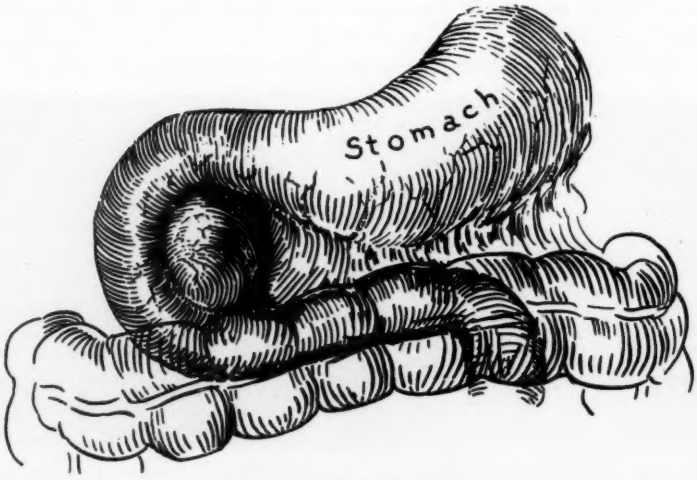

FIG. 7. Drawing of usual location and form of duodenal duplications. (In only 1 patient was cystic structure on outer curve of duodenum.)

FIG. 8. Photomicrograph of common wall between duodenum and duplication. Duodenal mucosa is on left and duplication lining is on right. Interlacing muscle fibers firmly unite these 2 structures.

most common of all, a spherical lesion, contiguous with some part of the bowel, particularly along the ileum (Figs. 5, 7, 11, 13).

At the operating table spherical lesions are recognized quite readily, but occasionally a long tubular duplication may be so incorporated in the intestinal or colonic wall that no abnormality is suspected. Such was the case in Patients 66 and 67 in whom the true nature of the lesion was manifested only after the sigmoid loop had been exteriorized (for a colostomy) and opened, revealing four lumina. The surgeon in both instances was not aware that this anomaly existed even though he had palpated the duplicated sigmoid during operation. In some of the long, tubular specimens, one sees a slight furrow between the anomaly and the contiguous gut (Fig. 10).

Variations in Size: Rounded duplications vary in diameter from 1 to 10 cm. or more. The tubular structures have been found as long as 65 cm.

Communications with Alimentary Tract: A communication was discovered between the duplication and alimentary tract lumen in only 13 instances, or 19%. Of the 13 thoracic lesions (not counting the three which arose from and communicated with the duodenum or jejunum), only one had an opening into the esophagus.

Differentiation from Mesenteric Cysts: Duplications found in the mesenteric leaves can be distinguished from mesenteric cysts without much difficulty. Simple lymphatic cysts are thin-walled and are usually flabby and loosely adherent to any surrounding structures, so that they can be peeled away rather easily; they are lined by flattened endothelial cells and the remaining portion of the wall is but a thin layer of fibrous connective tissue. In contrast, duplications almost invariably have walls about as thick as the adjacent bowel and

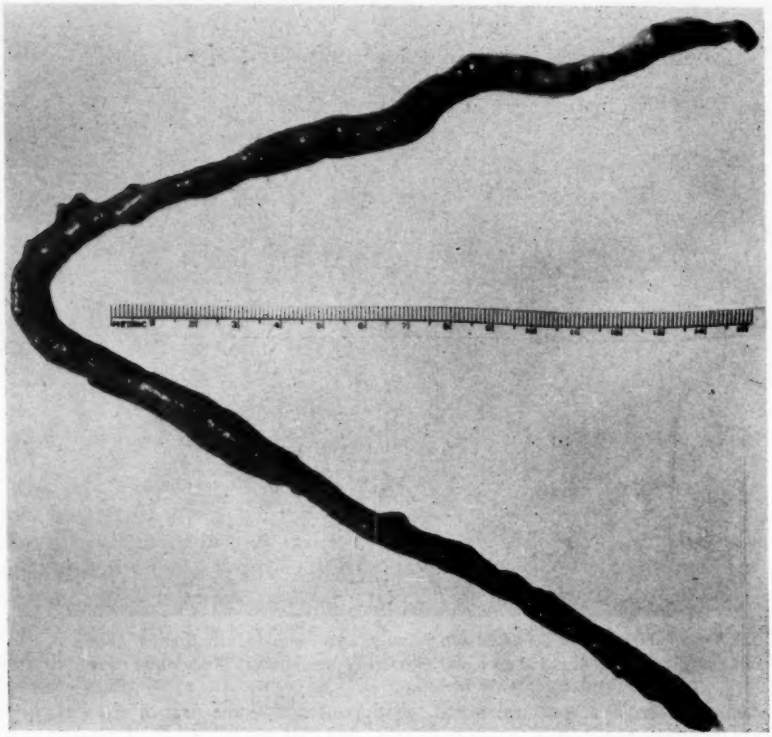

FIG. 9. Photograph of long single-lumened duplication which branched off from ileum, then coursed in between mesenteric leaves for short distance and ended blindly, with its distal tip unattached. Observe close similarity of this extra tube to normal small intestine.

microscopically there are various layers resembling the structure of esophagus, stomach, intestine, colon, etc.

Microscopic Appearance: The mucosal pattern of a duplication does not necessarily correspond to that of the adjacent alimentary tube. For instance, one tongue lesion and one esophageal duplication were lined with colonic mucosa, while gastric epithelium was found partially lining a rectal specimen and occasionally 2 or 3 different types of mucosa were observed in a single specimen. A few para-esophageal duplications have been lined with pseudostratified columnar epithelium but only one was ciliated. In some instances the epithelium is compressed to low cuboidal form, presumably from high intraluminal pressure of the entrapped fluid. Occasionally, a muscularis mucosa is common to both duplication and intestine; in many instances circular or longitudinal muscles are fused together. The mucosa may be denuded by acid juices which are present in some of the lesions. Whenever there has been gastric-like juice in the cyst, the wall is apt to be intensely inflamed from the sterile reaction.

Type Fluid: If there is a communication to the bowel, the contents of the duplication will, of course, resemble the material normally found in that particular segment of bowel. If no communication has existed, the fluid found in a duplication is usually clear, colorless and often mucoid. In many instances where a gastric lining is found, the cyst fluid is

TABLE B

ANOMALIES ASSOCIATED WITH DUPLICATIONS OF ALIMENTARY TRACT

Associated Abnormality	No. Cases Observed
Esophageal atresia	2
Situs inversus	1
Mongolism	1
Biliary atresia	1
Double gall bladder	1
Atresia of ileum	3
Omphalocele and exstrophy of bladder	2
Malrotation of intestine	5
Double uterus	2
Imperforate anus	3
Total	21

hemorrhagic, or is murky in color. Dark-colored fluid was also noted in several instances where gastric mucosa was not present; it probably resulted from destruction of the mucosa by great intra-luminal pressure.

Associated Anomalies: Surgeons always should be conscious of the fact that when one congenital anomaly exists others might be present also. This is well illustrated by this group of 67 patients in whom 21 associated congenital defects were noted (Table B).

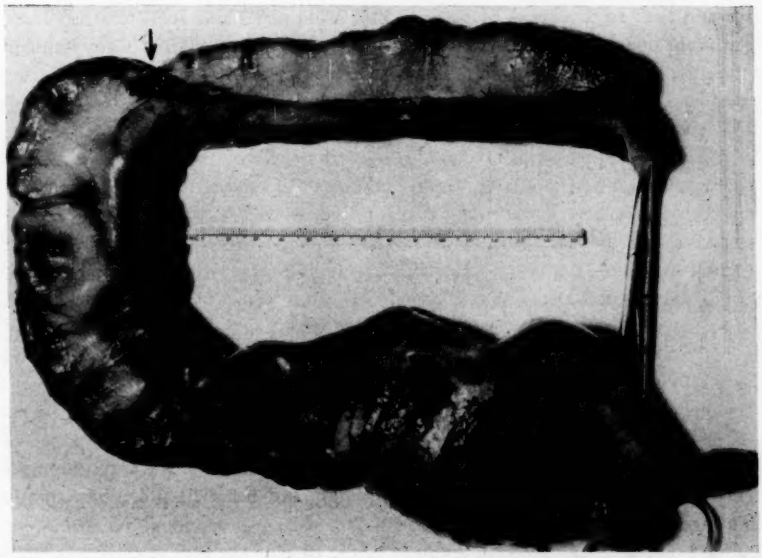

FIG. 10. Photograph of long duplication and its adjacent jejunum and ileum illustrating that occasionally it is possible to observe definite furrow at junction of congenital anomaly and normal bowel. Small intestine is structure having nearly same diameter throughout and hemostat clamped across one end. Arrow indicates site of perforation; transverse septum dividing duplication into 2 compartments was found just above this rent.

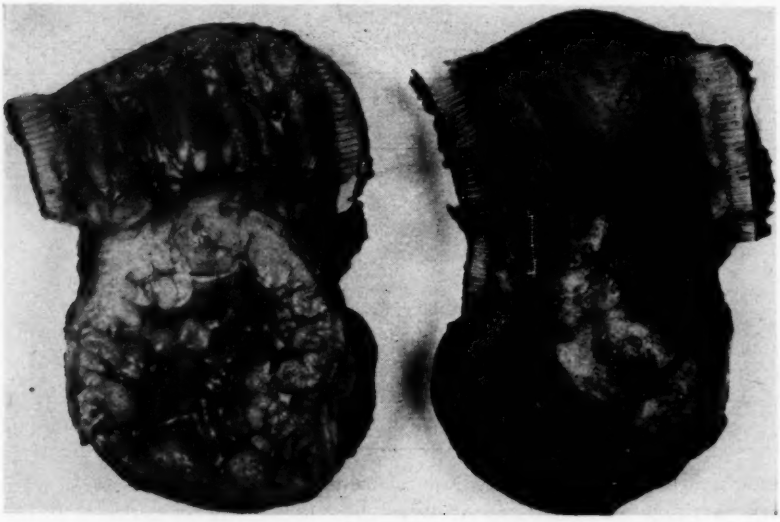

FIG. 11. Typical, small, spherical duplication found along terminal ileum. On left is internal view of duplication cut in cross section, while contiguous bowel is opened longitudinally. Note how impossible it would be to excise lesion without leaving defect in ileal wall. On right is external view of same lesion.

CLINICAL FEATURES

Age and Sex: In this series of patients 54% were males and 46% females. Their ages ranged from one day to 13 years. Fifty-one per cent of the children were younger than five months; half this group were less than one month. Only eight patients were over two years of age. This condition usually manifests itself early in life; however, Slomovitz et al.[10] reported a duplication of the ileum in a 55 year old man. Similarly, Loeffler and McDavid[11] observed an accessory colon in a 35 year old woman which measured 238 cm. in length. The fact that this latter lesion paralleled the colon and communicated with its lumen both proximally and distally explains the absence of symptoms in earlier life.

Symptoms and Physical Findings: In general, the most prominent symptoms are related to: (1) Obstruction—caused by intussusception or by a gradual expansion of the duplication and compression of the adjacent bowel; (2) Pain—from overdistention of the duplication or from an inflammatory reaction in neighboring viscera (when a duplication produces acid and proteolytic enzymes); (3) Gastrointestinal hemorrhage—from ulceration of the nearby intestinal tube. Bleeding can be attributed to erosion from gastric-like juices or it can come from interference with the vascular supply of the bowel when an expanding lesion lies within the mesenteric leaves.

Symptoms and physical findings vary greatly with the location of the duplications, hence it seems worth while to group patients accordingly and list their presenting complaints and findings.

Oral and Thoracic Cavities: An anomaly at the base of the tongue caused difficulty in swallowing and was easily palpable. There were 13 para-esophageal or pleural cavity duplications producing in some instances classical symptoms and physical findings of expanding intrathoracic lesions. Mild expiratory grunt, nonproductive cough, atelectasis, pneumonia

FIG. 12. RG of child with intestinal obstruction, subsequently found to be caused by duplication at ileocecal valve.

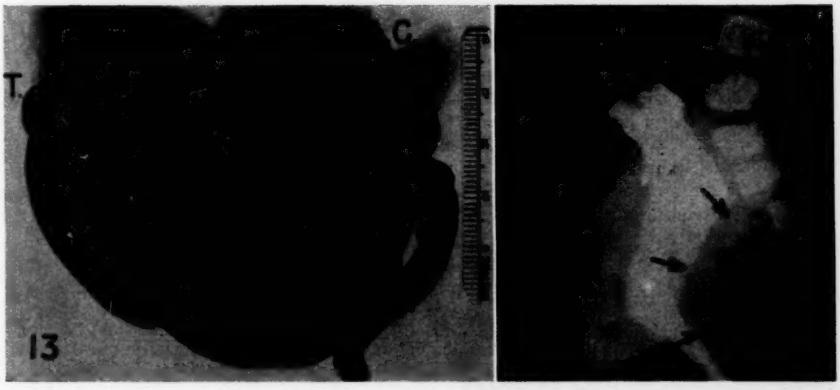

FIG. 13. Duplication at ileocecal junction which was completely excised along with cecum and short portions of terminal ileum and ascending colon. Smaller knob-like structures attached to tip of duplication proved to be 2 more duplicates, each having its own independent muscle and mucosal layers. Note how intimately duplication is fused with normal bowel. A., Appendix. A.C., ascending colon. Du., duplication. T.I., terminal ileum. T., triplication. Q., quadruplication.

FIG. 14. Lateral RG, with barium enema, showing marked anterior displacement of rectum by mass which proved to be duplication.

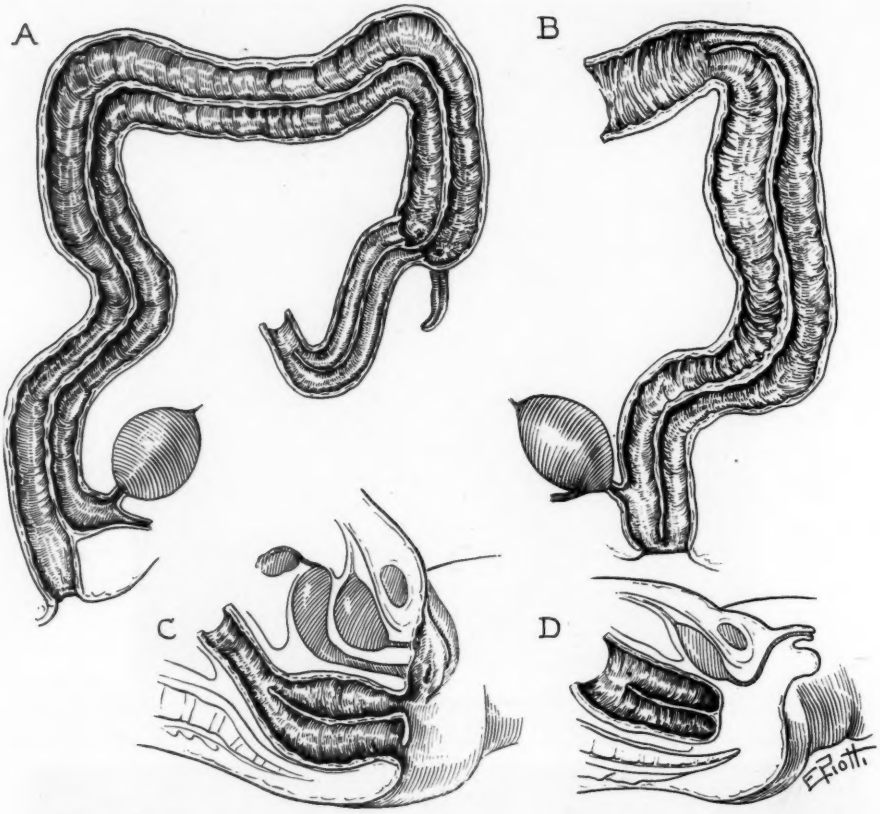

FIG. 15. Sketches of 4 double-barreled lesions of large bowel. In each, free communication existed proximally between normal colon and extra tube. In each, symptoms were caused by anomaly which existed at lower end of duplication. A. Patient had situs inversus, double terminal ileum, appendix, and entire colon. There was fistula from one rectal pouch (which was otherwise blind) to urethra. B. Recto-urethral fistula in patient with double large intestine extending from splenic flexure almost to anus. C. Extra rectal orifice discharging feces was discovered anterior to normal anus. D. Both duplication and normal rectum ended as imperforate structures.

and dysphagia were prominent features of several patients in this group. In four instances there were no related symptoms; the anomalies were discovered during routine chest roentgenographic examinations. Hematemesis and hemoptysis were the major complaints of Patient 9 (Table A) who had an esophageal duplication lined with gastric mucosa; the regional inflammatory reaction was so intense that there was erosion into the left upper lobe producing a bronchial fistula. It was necessary to perform a lobectomy along with excision of the duplication to effect a cure.

Thoracic Duplications Arising Below the Diaphragm: Three lesions (Cases 15, 16 and 17) are of special interest in that they arose from the duodenum or jejunum and entered the thoracic cavity. Coursing posteriorly and superiorly, they penetrated the posterior portion of the diaphragm and extended retropleurally, almost to the apex of either the

right or left pleural cavity. The abdominal portions resembled normal intestine but after entering the thorax all three assumed different forms and their diameters increased. In general, the symptoms in these three patients resulted from: (1) accumulation of gas and fluid within the thoracic segment of the duplication, giving cardio-respiratory distress; (2) secretion of hydrochloric acid and pepsin by gastric mucosa resulting in ulceration and gastrointestinal hemorrhage of almost exsanguinating degree; (3) production of intense reaction in the wall of the duplication and surrounding viscera by acid juices to such an extent that there was chest pain. Pertinent physical findings were limited to the chest where occasional peristaltic gurgles or coarse rales were audible. With the larger lesions, diminished breath sounds and dullness to percussion were found.

Stomach: One of these patients with a duplication of the stomach complained of epigastric fullness and pain but there was no evidence of obstruction, in spite of its enormous size. The other, an infant, had an esophageal atresia with a tracheoesophageal fistula and experienced no symptoms referable to the small stomach lesion, which was discovered and removed at the time a temporary gastrostomy was being performed.

Small Intestine: Symptoms and signs of intestinal obstruction, usually incomplete and also intermittent, were prominent features of several lesions located along the duodenum, jejunum and ileum. Obstruction just beyond the pylorus can arise from those duplications which are duodenal in origin. Two of our duodenal duplications had been marsupialized previously in other hospitals; both patients complained that vomiting and pain occurred if the mucus was not evacuated daily. One of the lesions had been marsupialized for eight years and the other one for five months, but neither showed tendency toward healing. The small spherical anomalies of the ileum, by gradually encroaching upon the intestinal lumen, produce obstruction and give vomiting, colicky pain, abdominal distention, hyper

FIG. 16. Barium-enema RG from patient with complete situs inversus, double terminal ileum and double colon.

FIG. 17. Barium enema revealing double-barreled duplication involving entire descending and sigmoid colon.

peristalsis, and at times melena. Obstruction occurs frequently at the ileocecal valve when a cystic lesion—even small—compresses the terminal ileum or the valve. Two duplications in this area served as leading points for intussusceptions. A duplication of the ileum was discovered accidentally in four instances while performing an operation for some other condition. When duplications take a spherical form they can usually be felt through the abdominal wall, but those which are tubular and elongated defy such detection.

Large Intestine: Duplications of the cecum gave rise to intussusception in two instances and severe gastrointestinal hemorrhage with anemia in another. The lesion found hanging from the transverse mesocolon produced no symptoms. There were four patients in whom double-barrelled tubular duplications occurred in the rectum or colon; in one of these there was an extension of this up along the terminal ileum. In each instance the extra lumen carried a fecal stream and the anomalous arrangement at the distal end of the duplication produced the symptoms which brought the patient to the hospital. In one, a female child, there was an accessory, anterior, perineal opening and feces extruded from both orifices. In another, the accessory lumen and the rectum itself both ended blindly several centimeters above the perineal skin. In the other two, both males, the extra colonic tube communicated with the posterior urethra, discharging feces into the latter.

Rectum: Three rectal duplications produced constipation and abdominal distention by pushing the rectum forward and obstructing it. Bloody stools had been observed in two of these patients. In each of the three cases a prominent mass was easily palpated by rectal examination.

Roentgenologic Examination

The first approach to a roentgenologic examination of the chest or abdomen should include plain films in the horizontal, upright, and lateral views. If this routine is followed, often one is rewarded with all the information necessary to arrive at a diagnosis without the necessity of using a contrast medium.

Duplications Arising Within the Thorax: Even though sufficient information for making an exact diagnosis may be lacking on plain films of the chest, it is usually possible to gain some idea of the general size and location of the mass. These lesions are located retropleurally and are close to the spine; they therefore must be differentiated from ganglioneuromas, neuroblastomas, neurofibromas and anterior meningoceles. If they are large, the heart and mediastinal structures are likely to be shifted toward the opposite side (Fig. 5). With barium in the esophagus, it is usually shown to be indented by the mass (Fig. 6). Only one of the lesions arising in the thorax had a communication with the esophagus; chest films failed to reveal air in the duplication. There may be intense inflammatory changes in the adjacent lung, or even in the contiguous part of the spine, when the duplication produces hydrochloric acid and enzymes which set up a regional, sterile reaction.

Thoracic Duplications Which Originate Below the Diaphragm: In each instance where a duplication was found to lie mostly within the thorax, but arose from within the abdomen, a communication existed with the bowel lumen. This permitted air and fluids to move up into the thoracic part of the duplication and these were evident upon fluoroscopic examination of the patients. When such a duplicated structure is coiled upon itself in the chest, the picture can easily be confused with that of a diaphragmatic hernia or, as in Case 17, actually a hernia might co-exist.

Stomach: When the seven year old girl with a stomach duplication was given a barium meal, she was found to have a large smooth indentation along the greater curvature and a barium enema showed the transverse colon displaced downward.

Small Intestine: Duodenal lesions produce partial obstruction, with dilatation of the

first part of the duodenum, compression of the second part, and delay in the passage of barium. With lesions located beyond the ligament of Treitz plain films of the abdomen, taken in appropriate views, often gave evidence of intestinal obstruction (Fig. 12). A duplication itself will be visualized on films only if quite large. It is rare to have barium enter the lumen of a duplication so that it can be identified, but this occurred in one of the jejunal lesions.

Large Intestine: Barium injected via an exteriorized sigmoid loop of bowel in two patients revealed the double lumens pictured in figures 16 and 17.

Rectum: A duplication lying posterior to the rectum must be differentiated from an anterior meningocele. The latter is suggested if films reveal a bony defect in the sacrum. A barium enema will be of assistance in identifying the most cephalad extension of the mass (Fig. 14). Sacrococcygeal teratomas similarly may push the rectum forward but this condition is usually accompanied by an external mass.

Treatment

All patients with duplications should be operated upon as soon as it is feasible. The operative procedure of choice varies according to the location of the lesion and the circumstances attending it. Nevertheless, two points should be borne in mind, both of which stress the importance of the surgeon's being thoroughly familiar with the pathology involved. First, it must be recognized that when a duplication is in contact with bowel wall there is seldom a line of cleavage between the two structures. Second, since these malformations (when appearing in relation to the small intestine) almost always lie on the mesenteric side of the jejunum or ileum, arteries and veins must course over their surfaces to supply the adjacent bowel.

While some duplications have been treated successfully in the past by marsupialization, the authors now believe that such a procedure is completely archaic and should never be employed. Whenever possible, an attempt should always be made to remove a cystic lesion in its entirety—a goal which can almost always be attained; only in rare instances does this objective have to be changed. Because the technical problems vary so widely from location to location, it is well to consider individually the duplications occurring at different levels.

Duplications Arising Within the Thorax: Formerly, these lesions were often treated by marsupialization, followed by attempts to destroy the mucosa by curettage, injection of caustic fluids, or by packing the cavity with gauze. Usually, it was necessary to repeat these destructive efforts on many occasions; this was a time-consuming, costly, and inefficient method of accomplishing the task, and furthermore it often led to considerable deformity of the chest wall and extensive fibrosis on one side of the thoracic cage. These multiple-stage procedures now have been abandoned in favor of a transpleural, complete excision of the lesion at one sitting. With care, a cyst can always be peeled away from the esophagus without serious injury to the latter; even if the esophagus is entered inadvertently it can still be repaired by appropriate suture and then covering the area with a flap of pleura.

Thoracic Duplications Arising Below the Diaphragm: The extent of the surgical undertaking depends upon the symptoms which have been present and the type of membrane which lines the duplication. When the complaints have been related entirely to distention of the intrathoracic portion of the anomaly and the lining is intestinal or colonic in type, it seems wise to remove only that segment which lies above the diaphragm (Cases 15 and 17, Table A). In contrast, if the symptoms have been those of hemorrhage and the lining is gastric in type, it is highly important to remove all the duplication.

including the infradiaphragmatic portion. Case 16, Table A, illustrates this point and fortunately it was possible to resect the abdominal and thoracic segments in one procedure, performing an end-to-end anastomosis of the jejunum.

Gastric Duplication: Treatment of large lesions associated with the stomach presents a difficult problem. One hesitates to perform a radical resection with esophago-jejunostomy in view of the accumulating evidence of marked nutritional disturbance which can follow this operation, particularly in childhood. Theoretically, it should be possible to excise the common wall between the two cavities, creating one large pouch. Probably the best method of therapy is excision of as much of the duplication as possible, and from any portion which remains to cut away the residual mucous membrane. The smaller lesions, especially those attached to the greater curvature, usually can be excised completely (Case 19, Table A).

Small Intestine Lesions: Duplications of the duodenum may be resected along with the first portion of the duodenum, followed by a posterior gastrojejunostomy as in Case 20, Table A; while successful in this patient, the authors do not now believe that such extensive surgery is necessary or justifiable. It is completely adequate to employ the method advocated by Gardner and Hart[12] (of removing a portion of the wall which lies toward the duodenum, creating a large opening between the two cavities). This orifice should be almost as long as the fused wall, to insure free exchange of *succus entericus* between the two structures at all times.

When confronted with duplications of the jejunum, ileum or certain portions of the colon, the ideal therapy in most instances is to remove the lesion, along with the contiguous intestine or colon, and reconstruct the alimentary tract by suitable anastomosis. Under some circumstances it is wiser and safer to avoid immediate union of the remaining intestinal ends and to exteriorize them in a Mikulicz fashion, subsequently crushing down the spur between the two loops.

Colon or Rectal Cysts: Right colectomy, followed by ileocolostomy, should be performed for lesions arising at the ileocecal valve or in the cecal wall.

For the three lesions posterior to the rectum, it was possible in all to perform an excision by making a curvilinear incision behind the anus, carrying the dissection upward in front of the sacrum until the mass was exposed. Two of the cysts could now be peeled away from the rectum without entering the latter, but in the third case the rectum was entered; it was repaired by infolding sutures and healed *per primam*.

Double-lumened Colon or Rectum: The authors' experience with four of these (Cases 65-68) indicates that it is not necessary to excise the entire lesion. Fecal streams can apparently be carried along both lumina with facility. It is necessary to attack only the lower end of the anomaly, which is the part which gives rise to symptoms. In Case 65 there was an imperforate anus which could have been repaired. In Case 68 the accessory rectal lumen opened externally through an additional anus anterior to the normal one; the two rectal lumina were made into a single cavity and the extra anus was closed. In Cases 66 and 67 the symptoms were related to discharge of fecal material from one rectal lumen into the posterior urethra; in each case the recto-urethral fistula was closed and the two rectal lumina were transformed into one cavity.

Results of Therapy: The increasing awareness of the problems presented by such anomalies, the application of newer concepts of chemotherapy and fluid and electrolyte balance, and the improvements in technics of intestinal surgery and anesthesia have all aided in substantially reducing the mortality rates for these patients. From 1928 through 1939, fatalities occurred in 27% of the authors' cases; in the next seven years this de-

creased to 18%. Since 1946 the figure has fallen to zero; in this last group were 20 patients, several of whom were extremely ill before coming to surgery.

Conclusions and Summary

The term "duplication" should be used when describing those spherical or tubular structures found along the alimentary tract whose walls contain well-developed muscular layers and whose lining is a mucosa similar to that of some part of the alimentary tract. They should not be confused with mesenteric lymphatic cysts, or anomalies arising from a Meckel's diverticulum.

Symptoms produced by these lesions usually vary according to their location, their size, and the type of fluid secreted by their mucosa.

Duplications should almost invariably be removed, even though they are incidentally discovered and have not as yet given rise to symptoms. The pitfalls met with surgical treatment of these lesions are discussed. In this series, cases treated prior to 1940 carried fatality rates which were quite high; in the 20 cases treated in the last four years there have been no deaths.

Sixty-eight examples of duplications from one institution are briefly listed; 45 of these have not appeared in the literature before. This amount of material coming from one hospital would seem to indicate that these abnormalities must occur with sufficient frequency to warrant the attention of pediatrician, roentgenologist, and surgeon so that they can be recognized promptly and treated suitably.

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Spanish Abstract

Duplicaciones del Tracto Digestivo

Las duplicaciones del tracto digestivo son estructuras esféricas o tubulares que poseen una capa bien desarrollada de músculo liso, recubierta por una membrana mucosa; se encuentran en todos los sitios desde la lengua al ano y están generalmente unidas en forma íntima a cualquier porción del tracto digestivo. Desde 1928 hasta 1950 hay registrados en el Hospital de Niños de Boston 67 enfermos con este padecimiento. Antes de 1940 solo había 18 casos, pero a partir de esta fecha se descubrieron 49 pacientes más. De esta serie 45 enfermos no han aparecido en ninguna publicación previa.

Se utiliza el término de duplicación del tracto digestivo por que simplifica la clasificación de dichas malformaciones. Es nuestra opinión que todas estas duplicaciones tienen un origen similar cualquiera que sea su localización.

Resumiendo las diversas localizaciones encontradas hubo: en la base de la lengua 1, con punto de partida y localización torácica 13; originándose por abajo del diafragma pero proyectándose en el tórax, 3; estómago, 2; duodeno, 4; yeyuno, 4; ileo, 20; area ileocecal, 8; colon transverso, 1; ciego, 3; sigmoides, 2; recto, 3; y lesiones cilíndricas dobles del colon o del recto en 4. Solamente en un paciente se encontraron duplicaciones múltiples.

Las duplicaciones asumen diversas formas, pero en la mayoría pueden incluirse en uno de los cuatro grupos siguientes: (1) tubular, partiendo del intestino y extendiéndose por alguna distancia entre las hojas mesentéricas; (2) cilíndricas dobles, (3) quísticas, que permanecen libres en la cavidad peritoneal, sujetas solo por una porción delgada del mesenterio (anomalía rara); y la mas común de todas que es la duplicación de forma esférica y que aparece contígua a una porción del intestino especialmente al ileo. El tamaño varía en el caso de las duplicaciones esféricas de 1 a 10 ó más centímetros. Las tubulares pueden tener hasta 65 centímetros.

Se encontró que existía comunicación entre la duplicación y el lumen del tubo digestivo solamente en 13 ocasiones o sea el 19%. Cuando no existe comunicación el líquido que se encuentra en la duplicación es generalmente incoloro, transparente y a menudo mucoso.

El 54% de los enfermos en esta serie fueron hombres y el 46% mujeres. Sus edades variaron desde un día a 13 años. El 51% eran menores de 5 meses y solo 8 enfermos fueron mayores de 2 años.

Los síntomas mas prominentes están en relación con: (1) obstrucción, causadas por invaginación o por la expansión gradual de la duplicación con compresión del intestino adyacente; (2) dolor, por sobre distensión de la duplicación o por reacción inflamatoria de las vísceras vecinas; (3) hemorragia gastrointestinal por ulceración del intestino o por interferencia con la circulación de éste.

Los síntomas y los datos de exploración física variaron con la localización de las duplicaciones. En las cavidades oral y torácica hubo: dificultad para la deglución en una anomalía en la base de la lengua. Estridor espiratorio leve, tos no productiva, atelectasia, neumonía y disfagia en las duplicaciones para-esofágicas o de la cavidad pleural. En 4 enfermos no había síntomas siendo descubiertas las anomalías por exámenes de rutina a los Rayos X. En un paciente hubo hematemesis y hemoptisis. En las duplicaciones torácicas con punto de partida abajo del diafragma hubo trastornos cardio-respiratorios, hemorragia gastro-intestinal y dolor torácico. Ocasionalmente se escucharon borborigmos o estertores gruesos así como disminución del murmullo vesicular y a la percusión, matidez. En las duplicaciones de estómago en un paciente no hubo síntomas y en el otro se presentó dolor epigástrico y sensación de plenitud. En el intestino delgado existieron síntomas y signos de obstrucción intestinal generalmente incompleta e intermitente. En el intestino grueso la duplicación dió lugar a invaginación o a hemorragia gastrointestinal severa. En los casos en que hubo duplicaciones cilíndricas dobles en el recto o en el colon, el lumen contenía materia fecal y la desembocadura anómala de la porción distal motivó la consulta. Las duplicaciones rectales originaron estreñimiento y distensión abdominal; observándose evacuaciones con sangre en 2 enfermos. El tacto rectal permitió palpar fácilmente la tumoración.

El examen radiológico debe incluir placas simples en posición horizontal, vertical y laterales. Cuando se observan a la fluoroscopia las duplicaciones torácicas originadas por abajo del diafragma es posible evidenciar aire y líquido en la porción intratorácica. La duplicación de estómago mostró después de la comida baritada una depresión a lo largo de la curvatura mayor y con el enema baritado se apreció desalojamiento del colon. El estudio radiológico en el caso de lesiones de intestino delgado revela signos de obstrucción parcial.

Todos los pacientes con duplicación deben operarse tan pronto como sea posible. El procedimiento operatorio varía de acuerdo con la localización de la lesión y con otras circunstancias relacionadas con ella. Siempre que sea posible debe tratarse de eliminarla en su totalidad y solo en raras ocasiones tendrá que modificarse este objetivo.

La mortalidad fué desde 1928 hasta 1939 de 27%; en los siguientes 7 años disminuyó a 18%; desde 1946 ha sido nula.

Por el número de enfermos presentados en esta publicación puede suponerse que dichas anomalías ocurren con la suficiente frecuencia como para garantizar la atención del pediatra, radiólogo y cirujano en tal forma que puedan ser identificadas prontamente y tratadas en forma adecuada.

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STUDIES ON ABNORMAL HEMOGLOBINS

IV. Persistence of Fetal Hemoglobin in the Erythrocytes of Normal Children

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VON KÖRBER[1] in 1866 and von Krüger[2] in 1887 demonstrated that hemoglobin solutions prepared from human placental blood exhibit a much greater resistance to denaturation with alkaline reagents than do specimens obtained from erythrocytes of normal adults. These observations have been repeatedly confirmed.[3–12] The hemoglobin of the newborn infant consists largely of fetal pigment (type F hemoglobin[13]) although a variable amount of the adult compound (type N) is always present.[14] The time required for the complete disappearance of the embryonic hemoglobin from the circulation has been reported to vary from 4 to 7 months after birth.[4, 5, 10, 11, 15]

Recent investigations[13, 16] in this laboratory furnished evidence that an alkali-resistant hemoglobin fraction is regularly encountered—irrespective of the age of the patient—in sickle cell anemia, and in the more fully developed syndrome of Mediterranean anemia. Irregularly, it may be found in hereditary spherocytosis and in some acquired hematologic disorders (acute and chronic leukemia, myelophthisic anemia, chronic aregenerative anemia). The hypothesis was advanced that this resistant hemoglobin fraction in the hereditary hemolytic syndromes may represent a continued production of the fetal pigment beyond the age during which it is physiologically present and that the appearance of the abnormal pigment in the "acquired" conditions may indicate a re-activation of such a mechanism.

Since the method for the detection of alkali-resistant hemoglobins employed in these studies[13] appears to be much more sensitive than the technics previously used, it was considered necessary to reinvestigate the problem of the time at which fetal pigment disappears from the circulation, under physiologic conditions, particularly since the demonstration of F hemoglobin at an age when it is no longer normally produced may suggest hematologic pathology of a more or less serious nature. The present communication deals with systematic determinations of the amounts of alkali-resistant pigment in 200 blood specimens collected at random from normal children varying in age from birth to six years.

MATERIAL AND METHODS

Twenty-eight cord blood specimens, taken immediately after delivery, and 172 samples from children up to the age of 6 yr. were tested. The samples were selected at random, except for omis-

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TABLE 1

No. of Specimens Examined at Different Age Groups

Age (mo.)	No. of specimens examined	No. of specimens having F hemoglobin
Cord blood	28	28
birth—3	11	11
4–6	11	10
7–12	25	19
13–18	32	15
19–24	7	5
25–30	15	6
31–36	5	1
37–48	26	3
49–60	23	1
61–72	17	0

sion of patients afflicted with disorders known to be associated with alkali-resistant hemoglobin fractions.[13] The age distribution of the children is given in table 1.

The technic of alkali denaturation used for the demonstration of F hemoglobin has been described in detail in previous publications of this series.[12, 14] Briefly, an approximate 10% hemoglobin solution is prepared from fresh oxalated or clotted blood, employing distilled water and toluene as hemolytic agents. 0.1 cc. of this hemoglobin solution is exposed to 1.6 cc. of N/12 NaOH. After the mixture has reacted for exactly 1 min. at 20° C., 3.4 cc. of a reagent which simultaneously precipitates the denatured chromogens and stops the reaction is introduced. The latter reagent is prepared by adding 1 cc. 10 N HCl to 400 cc. half saturated $(NH_4)_2SO_4$. The final mixture is immediately filtered and the hemoglobin concentration of the filtrate determined photometrically. The percentage of undenatured hemoglobin is then calculated and is referred to as the "One Minute Denaturation Value."

In a study of blood specimens from over 400 hematologically normal adult individuals,[12, 17] one minute denaturation values of from 0.5 to 1.7% have been found. Values of over 2% have been shown to be highly significant statistically,[13] and for the purpose of this report, any figure above this level was considered to indicate the presence of an alkali-resistant hemoglobin. Since none of the patients examined showed evidence of any of the diseases associated with pathologic presence of alkali-resistant pigments,[13] such a finding was interpreted to be due to the fetal compound.

Results and Discussion

The results of this investigation are plotted in chart 1. As can be seen from the scattergram, cord blood specimens contain from approximately 50 to 85% fetal hemoglobin. During the first three months of life, all the 11 infants examined (table 1) showed the fetal compound in amounts varying from 10.7 to 77.5% of their total hemoglobin. In the 4 to 6 months age group, 10 out of 11 specimens revealed quantities of F pigment from 3.3 to 19.0%, while during the second half of the first year of life, 19 out of 25 children still had from 2.7 to 27.1% of the embryonic pigment, the remainder revealing the presence of normal adult hemoglobin only. In the 1 to 2 years age group, about half the children (20 out of 39) persisted in their production of F hemoglobin, usually in amounts of 5% or less, but in two girls, being 12½ and 15 months old, one minute denaturation values of 20.2% and 15.7%, respectively, were demonstrable. In the 2 to 3 years age group 7 out of 20 individuals showed F hemoglobin in their red cells with a maximum value of 3.5%, all but one being under 30 months of age. From 3 to 5 years of age,

only 4 out of 49 children continued to show traces of embryonic pigment (up to 3.1%). No evidence for the presence of F hemoglobin was noted in 17 individuals 5 to 6 years old.

From these data it is readily seen that the percentage of the F compound rapidly decreases during the first year of life, is usually found in amounts less than 5% after this time, and is rarely demonstrable after the age of 30 months. Nevertheless, an occasional child continues to have small quantities of alkali-resistant hemoglobin as late as 4 years of age. In the few instances where this was observed, no evidence to suggest latent hematologic pathology was noticed, although it was not feasible to examine these

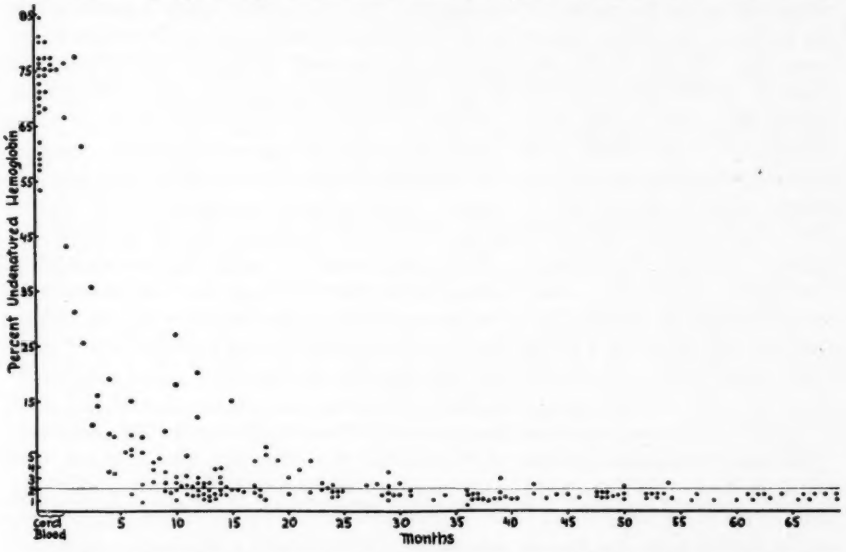

CHART 1. Scattergram of percentages of alkali-resistant hemoglobin found in specimens from 200 children from birth to 6 years of age. Horizontal line at 2% represents upper limit of values obtained in normal adults. Figures above this line represent F hemoglobin concentrations.

children with specialized hematologic technics. Whether some of these individuals represented instances of mild Mediterranean disease with minimal hematologic changes can not be stated with certainty. As reported previously,[13] some patients with thalassemia minor may show small quantities of an alkali-resistant pigment in hemoglobin solutions prepared from their erythrocytes. Other hematologic disorders found to be associated with alkali-resistant compounds (sickle cell anemia, hereditary spherocytosis, leukemia, etc.) could be definitely ruled out.

Previous investigations[4, 5, 10, 11, 15] of the replacement of fetal hemoglobin by the adult compound seemed to show that 4 to 7 months following birth the F compound is no longer detectable. The discrepancy between these results and those reported in the literature is most likely related to the method of alkali denaturation employed in identifying the embryonic pigment.[13] In previous studies, the percentage of F hemoglobin was determined by following the rate of denaturation of the hemoglobin solution over a period of time.[5, 6, 8–12, 18] By plotting the logarithm of the concentration of undenatured pigment against time, curves could be constructed which exhibited two main slopes, an ini-

tial steep portion representing the rapid denaturation of normal hemoglobin, and a second, more horizontal line, indicating the slower rate of destruction of the resistant components. By extrapolating the latter line to zero time, the concentration of the more resistant pigment can be estimated. With high percentages of fetal hemoglobin, this procedure yields excellent results. With concentrations of 5% or less of a resistant pigment, however, it becomes exceedingly difficult to draw a straight line through the lower portion of the curve, since the log of the concentration changes rapidly with minimal alterations in the amount of unaffected hemoglobin. In the present study, however, the technic employed permits the almost complete destruction of the normally denaturing compounds within the period of one minute.[13] The hemoglobin which is unaffected by this procedure represents, essentially, the percentage of resistant pigment present in the hemoglobin solution (minus the small quantity destroyed during the first minute). In numerous experiments involving artificial mixtures of normal and fetal hemoglobins, amounts of as little as 2% of the F fraction could be detected with accuracy.[17] Since more than 5% F hemoglobin is only rarely noted after the age of one year, the identification of such small quantities would be extremely difficult by the methods previously employed. Recently, Beaven and co-workers[15] have utilized electrophoretic and spectrophotometric technics to determine the quantity of fetal hemoglobin present in mixtures of the adult and embryonic pigments. Using the former procedure, approximately 10% F hemoglobin remained at 4 months of age in the few infants examined. No studies were carried out in older children. Since the electrophoretic technic employed can not demonstrate less than about 5% F hemoglobin, it seems unlikely that this procedure would show the persistence of this compound within this range beyond the age of one year. Similarly, using differences in the tryptophane line in the ultraviolet spectra of fetal and adult hemoglobins, concentrations of less than 10 to 20% F hemoglobin could not be identified.

That fetal hemoglobin continues to be produced, physiologically, after birth has been shown by Baar[8,9] who noted the reappearance of the embryonic compound following almost complete exchange transfusions in erythroblastotic infants. Furthermore, the continued production of this type of hemoglobin can be inferred from the data of Brinkman et al.[5] which indicate that the F pigment is still present in the circulating erythrocytes of some children at least as late as seven months of age. Since the life span of the normal adult red cell is approximately 120 days[19] (and that of the newborn infant possibly somewhat less[20]), F hemoglobin could be expected to be present in the circulation for not more than four months after its production ceases. From the present study it thus seems likely that F hemoglobin may continue to be formed, at least in some children, for longer periods of time than has previously been supposed.

No explanation is available for the noticeable individual differences in the disappearance time of fetal pigment. The mechanisms responsible for the shift from the production of F hemoglobin to that of type N are not yet understood. Whether F hemoglobin is principally a function of extramedullary hematopoiesis, or can also be manufactured in the marrow, remains to be elucidated. Further investigations will have to establish the factors which control the cessation of production of the fetal compound.

Summary

Two hundred specimens of hemoglobin, prepared from the blood of children up to the age of 6 years, were investigated for their content of fetal hemoglobin. Fetal hemoglobin was usually absent after the age of 30 months, although an occasional hemato-

logically normal individual was found to have minimal quantities of this pigment beyond this time.

The discrepancy between the results of the present investigation and data in the literature seem to be explained on the basis of the different methods used in identifying the embryonic pigment.

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SPANISH ABSTRACT

Estudios de Hemoglobinas Anormales. IV. Persistencia de la Hemoglobina Fetal en los Eritrocitos de Niños Normales

La importancia de esta investigación reside en el hecho de que, en estudios previos, los mismos autores han encontrado hemoglobina fetal,—en forma persistente y sin relación con la edad—en la

anemia de celulas en hoz, en el síndrome de anemia mediterránea, e irregularmente en la esferocitosis hereditaria, leucemias agudas y crónicas; anemias mieloptísicas y anemias crónicas arregenerativas, adelantando la hipótesis de que esta fracción de hemoglobina de los síndromes hemolíticos hereditarios pudiera representar la producción continua del pigmento fetal mas allá de la edad en la que se encuentra fisiológicamente y su aparición en los cuadros hemolíticos "adquiridos" una reactivación de dicho mecanismo. Además, es particularmente interesante demostrar si la presencia de hemoglobina fetal en edades fuera de los límites en que se produce normalmente puede sugerir un trastorno patológico hemático de naturaleza mas o menos seria. Por consiguiente consideraron necesario reinvestigar el término de tiempo en que, bajo condiciones fisiológicas, la hemoglobina fetal desaparece de la circulación y ratificar o rectificar usando un método mas sensible, los estudios previos que han asignado un lapso de 4 a 7 meses después del nacimiento.

El presente estudio comprende la determinación del contenido del pigmento fetal en 200 especímenes de hemoglobina preparados con la sangre de niños desde recien nacidos hasta la edad de 6 años incluyendo muestras de sangre extraída del cordón umbilical. El análisis de los datos obtenidos demuestra que la hemoglobina fetal generalmente desapareció después de los 30 meses de edad y solo ocasionalmente se encontraron cantidades mínimas de este pigmento en individuos normales después de dicha época.

La discrepancia de estos datos con los previamente reportados por otros autores es muy probable que sea debida al método empleado en la identificación del pigmento. Sabiendo que es indudable la producción fisiológica de hemoglobina fetal después del nacimiento, queda por explicar el mecanismo responsable del cambio en la elaboración de la hemoglobina fetal a la del tipo normal del adulto, la razon de las diferencias individuales en el tiempo de su desaparición de la circulación y si el pigmento fetal es principalmente función de la hematopoyesis extramedular o también puede ser de la medular, así como los factores que controlan la detención de la producción de la hemoglobina fetal.

29th Street and Ellis Avenue

ADRENAL CORTICAL HYPERFUNCTION IN CHILDHOOD

Report of a Case with Adrenocortical Hyperplasia and Testicular Adrenal Rests

By ELIZABETH KIRK ROSE, M.D., HORATIO T. ENTERLINE, M.D., JONATHAN E. RHOADS, M.D., AND EDWARD ROSE, M.D.
Philadelphia

THE following case of adrenal cortical hyperfunction with necropsy findings in a four year old boy is reported because of the rarity of this syndrome in children, and because of the finding of testicular adrenal rests.

CASE REPORT

J. S. was first seen at the age of 3 8/12 yr. His birth and early childhood until the age of 3 were uneventful (Fig. 1). At that time his parents became concerned because of adiposity associated with increased appetite. They also noted fatigability and lassitude. Soon afterward they observed hair growth across the shoulders and an axillary odor similar to that of an adult. He became increasingly preoccupied with food. Reduction of caloric intake, anorexogenic drugs and thyroid substances had been tried without avail. In 2 mo. his weight rose from 17.7 to 22.8 kg.

Examination showed striking obesity with round, rubicund cheeks, prominent abdomen, fat pads on shoulders and hips, heavy eyebrows and fine dark hair over the shoulders, upper arms and some in the axillary and pubic regions. No striae were present. His height was 92 cm., his weight 22.8 kg., blood pressure was 105 mm. systolic, 75 mm. diastolic. Genitals were normal in appearance. He was somewhat sluggish and negativistic. His appetite was voracious. He was admitted to the hospital for further study with the following findings: Hgb. 15.74 gm./100 cc.; RBC count 5.2 million/cmm.; WBC count 10.1 thousand/cmm.; neutrophiles, 62%; eosinophiles, 1%; monocytes, 2%; lymphocytes, 34%; hematocrit 49; BUN 13 mg.; serum cholesterol 271 mg.; fasting blood sugar 95 mg.; total protein, 6.6 gm., albumin 5 gm., globulin 1.6 gm./100 cc. Serologic tests for syphilis, glucose tolerance test and water excretion (Cutler-Power-Robinson) test were negative or normal. RGs of the long bones showed a slight delay in maturation. Pituitary fossa, skull and chest were normal. There was no evidence of osteoporosis. An intravenous urogram revealed a normally functioning urinary tract with no evidence of renal displacement or suprarenal masses. A 24 hr. collection of urine showed no gonadotropic activity, less than 13 mouse units of estrogens and 1.3 mg. of neutral 17-ketosteroids. Another determination 16 days later showed 4.9 mg. of neutral 17-ketosteroids/24 hr.

During the next 4 mo. an attempt to restrict his excessive caloric intake met with little success. The fourth month he suddenly became listless while at nursery school and complained of dull pain in his right flank. He became progressively less responsive, appeared confused and vomited after a small evening meal. His systolic blood pressure was found to be 140. The next day he remained unresponsive and complained of headache in the left parietal area; it was noted that his head tended to turn toward the left and there was impaired coordination of the left arm and leg. He was readmitted to the hospital (Fig. 2).

The patient's obesity and general appearance were unchanged, but the following new findings were noted: he was semistuporous, did not respond to questions or commands; there was a horizontal nystagmus with the fast component to the left; left abdominal reflexes were absent; there was a positive left Babinski; facial acne had appeared and the blood pressure was persistently elevated,

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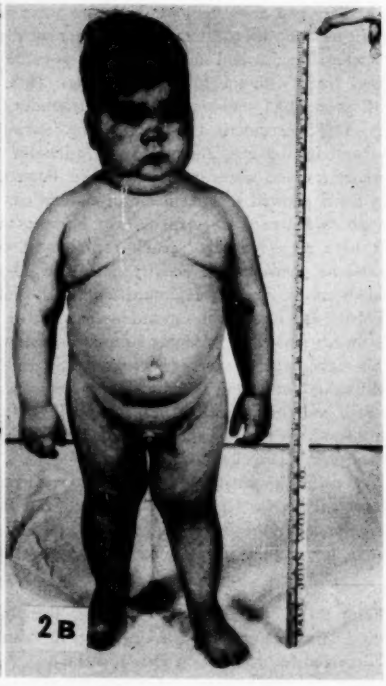
FIG. 1. J. S., aged 2 4/12 yr.
FIG. 2 A and B. J. S., before operation, aged 4 1/12 yr.



140 to 160 systolic, 110 to 120 diastolic. The ocular fundi were normal and examination of the cerebrospinal fluid showed no abnormality. The psychic and neurologic changes returned to normal in the next 3 days but the blood pressure remained elevated. Further studies showed the following: total eosinophile count was 3/cmm.; serum sodium 143 and 145 mEq. and serum potassium 3.1 and 3.4 mEq./l. The 24 hr. excretion of neutral 17-ketosteroids was 5.3 and 8.4 mg. on the 12th and 24th hospital days, respectively. Urinary corticoid excretion was 5.4, 4.3 and 5.3 mg./24 hr. on the 2nd, 11th and 20th hospital days, respectively. (Normal value is less than 1.5 mg. in this laboratory.) Oral glucose tolerance test showed a fasting blood sugar of 63 mg.; at ½ hr., 70 mg.; at 1 hr., 80 mg.; at 2 hr., 103 mg./100 cc. Intravenous glucose tolerance test showed a fasting blood sugar of 55 mg.; at 5 min., 299 mg.; at 20 min., 203 mg.; at 40 min., 135 mg.; at 60 min., 102 mg.; at 80 min., 79 mg./100 cc. RGs now showed generalized osteoporosis of the spine, pelvis and long bones. The subcutaneous injection of 5.5 mg. benzodioxane failed to produce a fall in blood pressure. Plasma CO_2 was 64 and 66 vol. %, plasma chlorides 99 and 103 mEq./l., BUN 9 mg./100 cc. Serum calcium determinations were 10.9 and 11.6 mg.; inorganic phosphorus 3.3 and 2.3 mg.; cholesterol 210 mg./100 cc. Repeated urinalyses were normal.

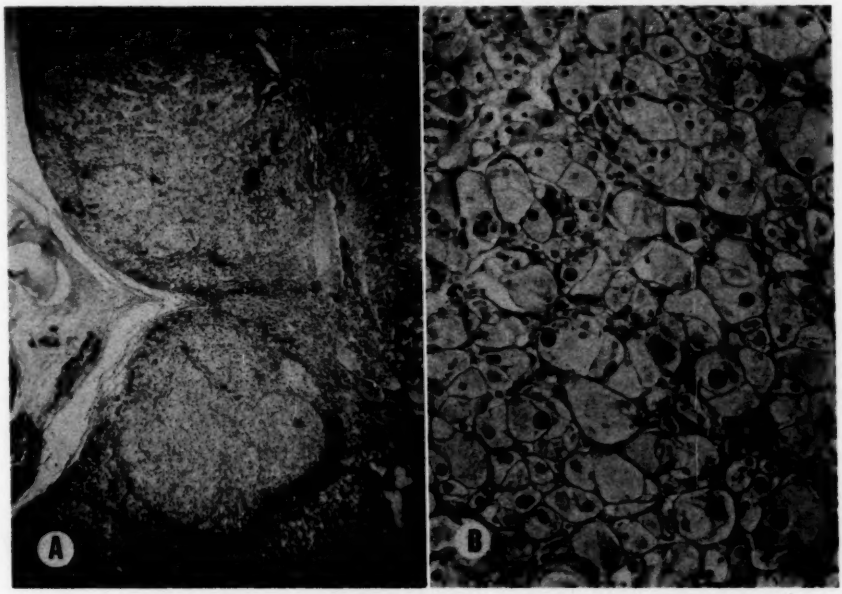


FIG. 3. Section of adrenal (A) removed at operation (×26), showing nodular hyperplasia (B) (×139).

It was now agreed that surgical exploration of the adrenals was indicated. This operation was performed by one of the authors (J. R.). Through a kidney incision the right side was explored. The right adrenal was found to measure approximately 3 x 1.5 x 1 cm. Except for its size it appeared grossly normal. About one-fourth of it was resected. The left adrenal region was next explored through a similar incision. The left adrenal appeared about twice the size of the right adrenal, somewhat nodular and about two-thirds of it was resected. The patient received 5 cc. aqueous adrenal cortical extract intramuscularly every 6 hr. for 3 days after operation along with intravenous glucose and normal saline. There was no evidence of adrenocortical insufficiency. During this time the blood pressure remained elevated 130 to 160 systolic, 90 to 120 diastolic. The postoperative course was marked by persistence of tachycardia and fever for about 14 days. On the third postoperative day the total eosinophile count was 12/cmm.

Examination of the excised adrenal tissue was reported from the laboratory of Dr. Robert C. Horn as follows: "The specimen consists of two portions, the first a biopsy from the right adrenal measur-

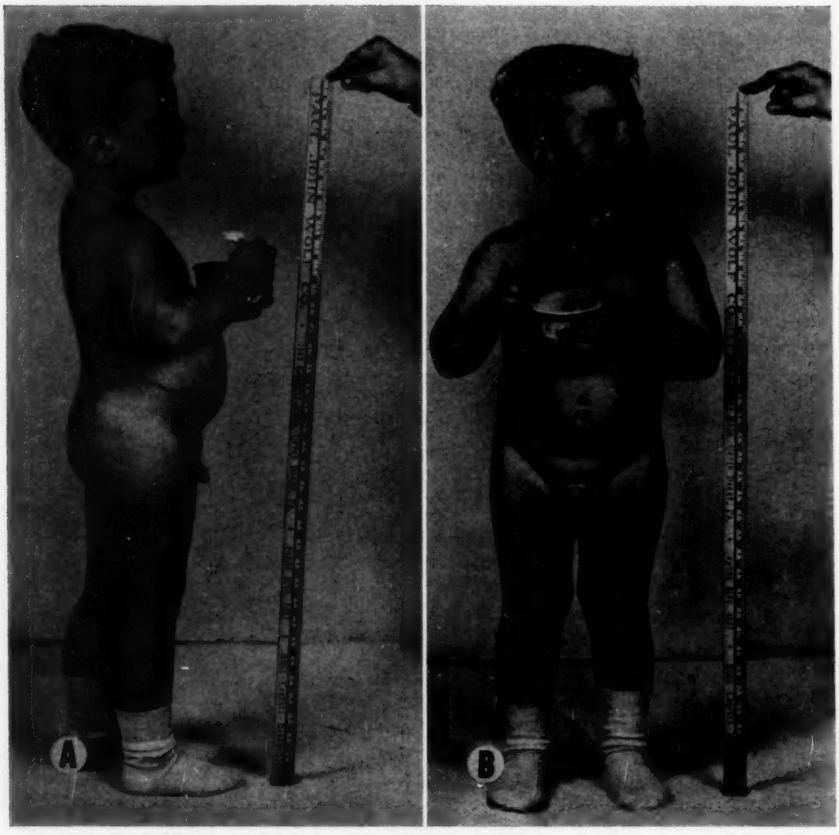


FIG. 4 A and B. J. S., after operation, aged 4 6/12 yr.

ing .2 x .8 x .8 cm. and the second a biopsy of the left adrenal measuring 2 x 1.2 x .8 cm., weighing together 6 gm.

"The right adrenal biopsy consists of red-brown tissue which is rather soft and in several small areas appears hemorrhagic.

"The left adrenal biopsy consists of golden brown to mud colored parenchyma in triangular shape with a flat base. The tissue has a rather nodular consistency but seems well encapsulated.

"Microscopic: Sections of the right adrenal reveal at one point, the three layers of the cortex. Cells of all three layers show regular size and nuclei but many of each layer show foamy, vacuolated cytoplasm with lacy threads of eosinophilic cytoplasm scattered through, but not completely packing the cells. However, through the greater portion of the sections, these near-normal cells are compressed and displaced by large nests and sheets of eosinophilic cells arranged in columns and short cords of cuboid cells, moderately large, with foamy, lacy pink cytoplasm not entirely filling the cells. The nuclei are regular, round, moderately large and contain basophilic granular chromatin material and one eccentrically disposed prominent dark bluish nucleolus. No mitoses are seen in any cell layer although several dinucleate cells are seen. These nests of cells seem sharply demarcated from the cells of the normal layers and no invasion of them is seen. An erythematous border appears around the junction with occasional small areas of hemorrhage. No medulla appears." (See Fig. 3.)

"Sections of the left adrenal reveal the same picture with the additional presence of medulla, the

cells of which also show vacuolated, foamy cytoplasm although the nuclei are regular. Interposed here are small sinusoidal blood spaces and a few ganglion cells.

"Diagnosis: Hyperplasia of adrenal cortex."

Following the operation the changes were gradual, but striking. Within 1 mo. he became alert, at 6 wk. the acne had disappeared, a decrease in the hirsuitism was noticeable and his mother reported more interest in other children, less fatigability and a relative indifference to food. Seven weeks after operation his 24 hr. urinary corticoid excretion had fallen to 1.9 mg. By 2 mo. his weight had fallen from 22.7 to 20.0 kg. The contour of his face and body had changed (Fig. 4). After 2½ mo. his blood pressure returned to normal. RGs showed recalcification of the skeleton. He remained improved and enjoyed normal health.

Four months after operation he was readmitted to the hospital following an episode of drowsiness, fever, right parietal headache and vomiting accompanied by an episodic rotation of the head to the left and left superior rotation of the eyes. Acute pharyngitis and tonsillitis became manifest within 24 hr. His blood pressure was 110 systolic, 72 diastolic. On admission Hgb. was 11.2 gm./100 cc., RBC count 3.9 million/cmm., WBC count 12.0/cmm. with 71% neutrophiles, 2% eosinophiles, 10% monocytes and 17% lymphocytes. Three days later when afebrile, the WBC count was 6.8 thousand/cmm. The total eosinophile count was 162 and fell to 131/cmm. 4 hr. after epinephrine injection.

The oral glucose tolerance test gave the following values: fasting 59 mg.; ½ hr., 93 mg.; 1 hr., 63 mg.; and 2 hr. 45 mg./100 cc. The 24 hr. neutral 17-ketosteroid excretion had fallen to 2.1 mg. The neurologic examination and EEG were normal.

Three months later, there occurred another brief episode of abdominal pain with vomiting, deviation of the head and eyes. Two months later, his height had increased to 99 cm. and his weight to 21.3 kg. His parents reported increased aggressiveness and appetite. His blood pressure remained normal, 105 systolic, 72 diastolic. His abdomen seemed more obese, his eyebrows thicker and heavier. He had complained of occasional headache followed by drowsiness.

One month later, Hgb. was 13.3 gm., WBC count was 14.0 thousand/cmm. and 72 eosinophiles/cm.

Four days later, he complained of headache and malaise. There soon followed a series of generalized convulsions with intervening drowsiness and fever. Several episodes of vomiting occurred, with massive hematemesis and melena. The preceding day, he had complained of pain in the cheeks. (Later it was learned that he and a companion had been exposed to epidemic parotitis. The latter developed the disease 2 wk. previous to the day the patient became ill.) On admission to the hospital his temperature was 41.0° C., blood pressure 130 systolic, 90 diastolic. He died 9 hr. later without regaining consciousness.

Necropsy was performed 13 hr. after death. The body was that of a 5 yr. old white male, moderately obese with a chiefly truncal obesity. There was a generalized livor mortis; abdominal striae were not apparent though faint striations of the adductor surface of the thigh were present. There were healed 12 cm. cicatrices in both costovertebral angles. There was no pubic or axillary hair. Penile development was normal for his age. Both testicles were in the scrotum.

The significant findings were as follows: all visceral organs showed a marked hyperemia. The heart and vascular system were not remarkable. The laryngeal mucosa was edematous with narrowing of the airway. The trachea and bronchi were injected and contained bloody mucinous material. The pleura were dark red. The consistency of all lung lobes was that of liver save for a few small crepitant pale areas in the upper lobes. On section, the lung surface oozed a serosanguineous fluid.

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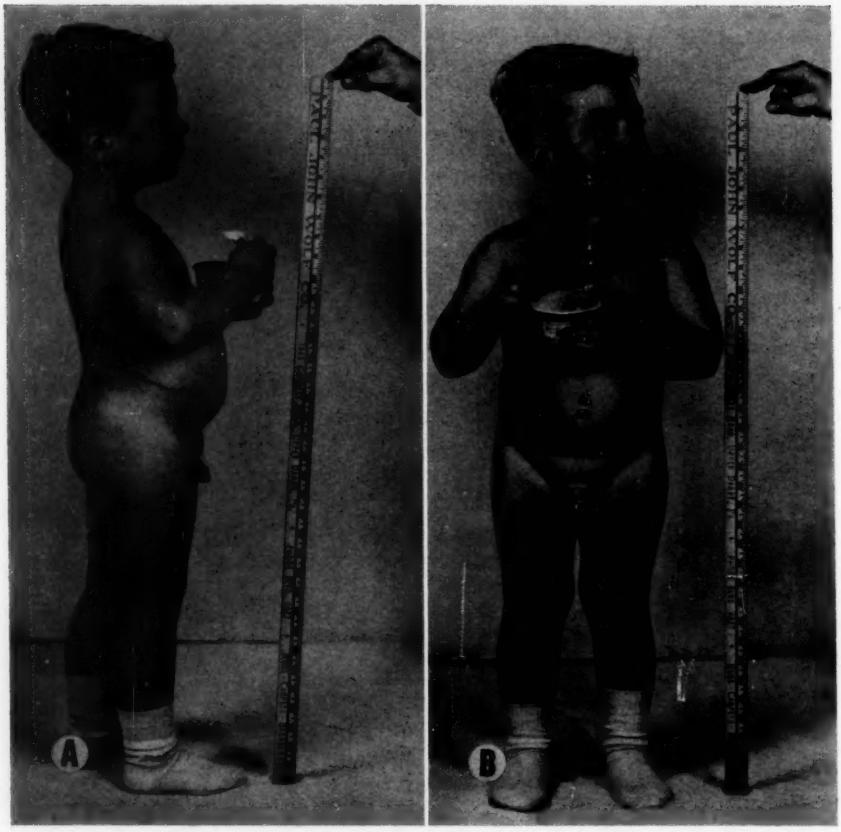

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prominent in the medulla. Hassall's corpuscles were large and formed minute keratin cysts. Polymorphonuclear cells and eosinophiles were present in moderate numbers. The spleen weighed 130 gm. It was dark red, and on section the pulp was diffluent. Microscopically the red pulp was engorged with blood, the follicles were large with large numbers of macrophages and polymorphonuclear cells.

The lymph nodes were not prominent. Microscopically there were lymphocytic depletion with foci of necrosis in germinal centers and reticuloendothelial hyperplasia. There was considerable edema, and the sinuses were filled with cellular debris similar to that in the germinal centers.

The bone marrow showed moderate granulocytic hyperplasia. Megakaryocytes were numerous though their nuclei were for the most part pyknotic. Osteoblastic activity appeared reduced. Hematopoietic marrow was abundant in the sites examined (lumbar vertebrae, sternum, rib).

The pituitary weighed 0.28 gm. It was symmetric without gross tumor. It was fixed in Zenker's and stained with hematoxylin and eosin, and with Mallory trichrome. Microscopically no tumor was present, nor could Crooke's changes be demonstrated with certainty. An occasional basophil cell showed vacuolization but no hyalinization. There appeared to be no striking alteration in the relative frequency of basophils, chromophils and chromophobic cells. Gross serial section of the pituitary failed to reveal any adenomatous areas.

The thyroid weighed 6 gm. It was soft, pale pink, and without nodulations. Microscopically there was considerable variation of acinar size. The epithelium was low cuboidal. Colloid was abundant with scanty peripheral vacuolization.

The parathyroids were not grossly enlarged. They were composed of principal cells almost entirely. Wasserhelle cells were rare and oxyphil cells were not seen.

The pancreas was not grossly remarkable; however, it had undergone considerable autolysis and alveolar detail of the islet cells was too poor for evaluation.

The adrenals weighed 2.1 gm., left, and 2.5 gm., right. Both were adherent to surrounding structures by dense adhesions resulting from the previous surgery. The left was roughly cuboidal, the right triangular and flattened. The cortex bilaterally was distorted by adhesions and beaded with yellow nodulation. The medulla was not prominent. A portion was fixed in Zenker's, the remainder in 10% formalin. Sections were stained by hematoxylin and eosin, Mallory trichrome, iron and Sudan IV.

Microscopically the glomerulosa was pale and narrow with vacuolated cytoplasm and spherical nuclei. The fascicular zone was reduced to cords of cells with prominent moderately pyknotic nuclei and scanty, finely vacuolated cytoplasm. These cords separated nodules which made up approximately two-thirds of the cortex. The cells of these were large, rounded to polygonal and varying considerably in size. The nuclei were round to oval. Nucleoli were not prominent. The cytoplasm was eosinophilic and rather granular, with varying amounts of fine vacuolizations. Occasional cells were gigantic with huge, though regular, nuclei. Binucleate cells were common. Many contained a fine golden brown pigment which failed to take stains for iron, lipid, or to reduce silver. On fat stain the glomerulosa took the stain heavily, the fascicular zone variably and the hyperplastic nodules quite lightly, with fine sudanophilic droplets, though an occasional cell took the stain heavily. These nodules gave the appearance of arising from the reticularis or inner fascicular zone, since the intervening cords of fascicularis were displaced laterally and toward the cortical surface.

The testicles weighed 6 gm. each. These were not externally distorted. On section, however, the left testicle showed 2 small brown nodules, one about 3 mm., the other 7 mm. in diameter (Fig. 5). These were in the rete testis area and stood out from the pinkish surfaces of the uninvolved portion of the testicle. In the right testicle was a similar, though single, nodule in the same position. Histologic examination revealed the seminiferous tubules to be lined with Sertoli cells with an occasional primary spermatogonium. Interstitial cells were scanty. The rete tubules were distorted by masses of cells similar to those in the adrenal. They were arranged in a vascular stroma. They were large eosinophilic, slightly vacuolated, variable in size. The nuclei were spherical to oval with prominent nucleoli. Golden brown pigment was present in the cytoplasm. Crystalloids were not seen. Sudanophilic droplets were present though minute and scanty. The pigment did not take iron stain, reduce silver, or stain with Sudan IV. The chief differences were the greater amount of nuclear variations, the presence of prominent nucleoli, and the lesser amount of sudanophilic material in the cytoplasm.

Histologic study of the brain was undertaken by the late Dr. F. H. Lewey. He verbally reported the

presence of hypothalamic lesions, but his untimely death interrupted his study of the sections. Unfortunately an exhaustive search has failed to reveal any notes by Dr. Lewey relating to these lesions and the sections presumably containing the lesions have also been lost. Loss of these sections of the hypothalamus is most unfortunate in view of their possible importance in relation to the pathogenesis of the adrenocortical hyperplasia.

This case at autopsy showed bizarre bilateral nodular hyperplasia of the adrenal cortex. The adrenals closely resembled the adrenal tissue removed surgically 9 mo. before death. The hyperplastic nodules arose at multiple points from the inner fascicular or reticular zones. This hyperplasia was not similar to the occasional nodulations found in infants with adrenal cortical hyperplasia associated with virilism and hypertension. Bilateral nodules were present here in the rete testes. These were

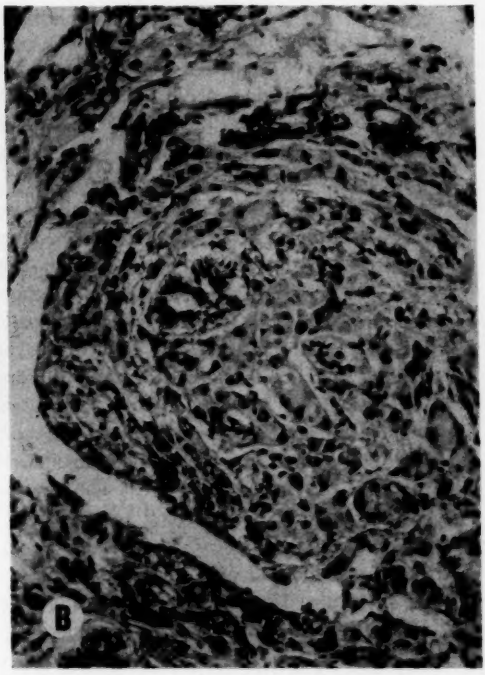

Fig. 5. A. Testis, showing nodule. B. Section showing adrenal rest cells about rete tubule ×154.

considered adrenal rests rather than an interstitial cell tumor of the testes for the following reasons: (1) the cells cytologically were similar to those of the adrenal and stained similarly with a variety of fat and other special stains; (2) crystalloids could not be identified; (3) the area of the rete is described by Freeman[1] as a frequent site of adrenal rests; and (4) virilism was not a prominent feature of the case as would be expected if the lesions represented an interstitial cell adenoma.[2]

The pituitary was not enlarged and contained neither adenomata nor Crooke's changes in the basophils. The immediate cause of death was massive hemorrhage from ulceration of the esophagus and gastric mucosa with aspiration of blood into the pulmonary tree.

Adrenal cortical hyperfunction is rarely encountered in childhood. Wilkins[3] and Williams[4] imply that the syndrome occurring before the age of 10 years is always associated with adrenal cortical tumor, and the latter cites 26 such cases collected up to 1948. In 1949, Chute, Robinson and Donohue[5] reviewed the verified cases, discussed the pathology and abnormal physiology of the syndrome and reported an additional case. Their patient was an 8 year old white girl with bilateral nodular hyperplasia of the adrenal

cortexes and Crooke's changes in the basophile cells of the anterior pituitary. They accepted 33 cases as authentic. The age of onset varied from 5 months to 15 years. The most consistently reported pathologic change was the presence of the hyaline degeneration of Crooke in the basophile cells of the anterior pituitary. This was reported to be present in all the 11 cases in which search for it was mentioned. Pituitary adenomata were reported in 7 cases (6 basophilic, 1 not specified). Hyperplasia, adenomata or carcinoma (in 7) of one or both adrenal cortexes was described in 13 of the 18 cases. The youngest patient was 8 months old at death and symptoms had been present 4 months. In 7 of the 10 males the gonadal changes mentioned included atrophy (2), increase in interstitial tissue (1), enlargement of the testes (1), suppressed spermatogenesis (1), infantile (1), normal (1).

Follis[6] in 1951 reported a 15½ month white male infant with evidence of adrenal cortical hyperfunction, obesity, hirsutism, facial comedones, thin skin, but with normal genitals. There was no mention of blood pressure or glucose tolerance. Death followed exploratory laparotomy. Necropsy showed localized accumulations of basophilic cells in the hypophysis (Crooke's changes were not mentioned), adrenal hyperplasia, loss of lymphocytes from thymus and spleen, and a chondrodystrophic type of lesion of the ribs.

The occurrence of heterotopic adrenal tissue in the testes has not been frequently reported, and the authors have found no instance of such heterotopia mentioned in association with adrenal cortical hyperfunction. Freeman,[1] in 1945, reviewed the literature and reported a case in a 73 year old male. She states that insufficient data are available to determine the incidence of such rests, but suggests that they may be more common in infancy and that they may progressively disappear thereafter.

Several aspects of the authors' case warrant speculation or comment. Despite the bulimia, rapid weight gain, hirsutism and axillary odor, the authors were at first misled into a diagnosis of simple exogenous obesity and did not seriously consider an endocrinopathy until the second assay of 24 hour neutral 17-ketosteroids excretion was reported. As is so often the case several components of the classical picture of adrenal cortical hyperfunction were absent. These included impairment of glucose tolerance, genital dystrophy, striation and polycythemia. The cause of the neurologic signs and symptoms remains obscure. The changes in the patient's personality, physical habitus and appetite after partial adrenalectomy were striking. The cause of the esophageal ulceration, which led to the fatal massive hemorrhage, remains uncertain. Uncertain also is the role of an overwhelming virus infection. (Possible prodromal stage of epidemic parotitis is difficult to evaluate in this instance.) Gastrointestinal hemorrhage occasionally accompanies both experimental and clinical shock. It is possible that a partial selective adrenocortical insufficiency coexisted with the manifestations of cortical dysfunction and hyperfunction, and impaired the patient's ability to resist the stress of an overwhelming infection.

The loss of the hypothalamic tissue sections was most unfortunate and may possibly have deprived the authors of a bit of confirmatory evidence supporting Heinbecker's concept[7] of the hypothalamic genesis of adrenal cortical hyperfunction. One is tempted to speculate on the possible significance of the relationship between the apparent absence of abnormalities of impairment of glucose metabolism and the restriction of the adrenal lesions to the fascicular and reticular zones. However, the lack of knowledge concerning the cellular origin of the various cortical hormones permits no conclusion.

Summary

An additional case of adrenal cortical hyperfunction occurring in a boy aged 3 8/12 years is reported. The clinical features included bulimia, obesity, hypertension, hirsutism, personality change, osteoporosis and intermittent neurologic manifestations. The urinary excretion of 17-ketosteroids and corticoids was increased. There was no genital dystrophy or impairment of glucose tolerance. Marked temporary improvement followed partial bilateral resection of the enlarged adrenals. The patient died 10 months after operation, following exposure to epidemic parotitis, as a result of massive hemorrhage from ulceration of the esophagus. Necropsy showed bilateral nodular adrenal cortical hyperplasia limited to the fascicular and reticular zones. Bilateral rests of adrenocortical cells were found in the rete testis. No Crooke's changes or adenomata were found in the basophile cells of the anterior pituitary.

Addendum

Since the above paper was submitted for publication, Landing and Gold (Landing, B. H., and Gold, E., Leydig cell proliferation in familial adrenal cortical hyperplasia, J. Clin. Endocrinol. **11**:1436, 1951) have described three male infants with congenital adrenal cortical hyperplasia who also presented nodular proliferation of Leydig cells in the hilum and rete testis. They suggest that the previously reported cases of adrenal rests in the testis may actually have represented similiar collections of Leydig cells. In the present authors' case, however, there seems little doubt that adrenal cell rests were present in the testis.

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Spanish Abstract

Sindrome de Hiperfuncionamiento Adrenocortical en Niños; Reporte de un Caso con Hiperplasia Adrenocortical y Restos Adrenales en los Testiculos

Se reporta un caso de hiperfuncionamiento adrenocortical ocurrido en un niño de tres años y ocho meses de edad. El cuadro clinico presentaba: bulimia, hipertensión, hirsutismo, cambios de la personalidad, osteoporosis y manifestaciones neurológicas intermitentes. La excreción urinaria de los 17-ketoesteroides y corticoides estuvo aumentada. No sé observó distrofia genital, ni tampoco alteraciones en la tolerancia a la glucosa. La resección parcial bilateral de las glandulas suprarenales resultó en una mejoria clinica marcada de caracter transitorio. El paciente falleció diez meses después de la operación a consecuencia de una hemorragia masiva causada por una ulcera del esofago. El

estudio necropsico de este paciente reveló una hiperplasia cortical nodular bilateral de las zonas fascicular y reticular de las suprarenales. Se notaron restos de tejido adrenal en ambos testiculos. No se observaron cambios de Crooke o adenomatas en las celulas basofilas del lobulo anterior de la hipofisis.

213 Maloney Clinic, Hospital of the
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EFFECTS OF EARLY FEEDING OF STRAINED MEAT TO PREMATURELY BORN INFANTS

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THE addition of strained meat to the diet of full term infants has been reported to improve their general well being and promote red blood cell and hemoglobin formation.[1] The present study was undertaken to determine whether the addition of strained meat to the diet of prematurely born infants would have similar effects. In addition this study was planned to measure the effect of a marked increase in the protein intake upon growth in weight and length, and upon the serum protein concentration of such infants.

Meat has been used in formulae partially or completely to replace milk proteins.[2] Additions of strained meat to the formulae of premature infants in the first month of life are well tolerated, and the meat protein is "as well retained and utilized as milk protein."[3]

In the present study, one group of infants receiving a proprietary milk formula designed especially for premature infants (control group) was compared with another group receiving an identical formula to which strained meat was added (experimental group). These two groups were further compared with a third group of infants who were breast fed and received no meat supplement (breast-fed group).

The study was conducted from July 1948 to May 1950. The effect of seasonal variation was reduced by pooling results over this period of time.

MATERIALS AND METHODS

One hundred and forty-four infants were included in this study. They were selected from those who were admitted to the premature clinic after discharge from the premature nursery in Sarah Morris Hospital. The infants were discharged from the premature nursery when they attained a weight of about 2000 gm.

The distribution as to diet was determined as follows. Infants who were not being breast fed were placed on the formulae described below. The decision as to whether an infant was to be placed in the experimental group or the control group was based solely upon the desire to maintain a 2:1 ratio in the number of subjects in the 2 groups. All those infants who were completely breast fed at the time of their first clinic visit and who continued thus for 6 wk. or longer were considered in the breast-fed group. These infants received no supplementary meat. An even distribution by race and sex was maintained in the various groups.

Infants were excluded from the study whenever for any reason they were not examined within 30 days of the previous visit; whenever there was a deviation from the prescribed diet for a period of 7 days or more; or whenever a chronic illness occurred which appeared to be unrelated to the feedings and which might affect growth.

From the Kunstadter Laboratories for Pediatric Research, the Department of Pediatrics, Sarah Morris Hospital for Children, and the Mandel Clinic, all of Michael Reese Hospital, Chicago. The premature clinic of Mandel Clinic is supported in part by the Infants' Aid Society of Chicago.

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The control group was fed a formula containing 10 tablespoons of olac®* added to 20 oz. of boiled water. This formula provides 0.95 gm. of protein/fluid oz. and 19 cal./fluid oz. The experimental group received a formula containing 1 can (approximately 3 oz.) of Swift's strained meat† (beef, liver, lamb, veal or beef heart) and 10 tablespoons of olac® added to 17 oz. of boiled water. The protein content of the experimental formula was 1.7 gm./fluid oz. (approximately twice that of the control) and the caloric value 24 cal./fluid oz. These figures varied only slightly with the variety of meat used. All the mothers were instructed to feed the infant as much as he would take without urging. The daily intake was measured by the mother and reported to the examining physician at each visit.

All the infants of the 3 groups received similar vitamins, iron supplements and solid foods. During the 1st 5 mo. of study, each infant received oleum percomorphum, 15 drops twice daily and ascorbic acid, 25 mg. daily. After that period, 3 teaspoonsful daily of polyvitamin dispersion® were substituted. During the 1st 7 mo. of the study, ferrous glycinate supplying 10 mg. of metallic iron was given daily. After that, iron ammonium citrate was given to supply 32 mg. of metallic iron daily. Analysis of the data revealed no significant difference in the values for Hgb. and RBC count between infants receiving the 2 different iron preparations. At 3 mo. of age the infants were given cereal once daily; at 4 mo. cereal twice daily; at 5 mo. vegetables were begun, at 6 mo. egg yolk and at 7 mo. fruit. During the 2nd 6 mo. of the infant's life and after a weight of 6750 gm. was attained, the diets of all 3 groups were essentially the same.

Observations were made at 2 wk. intervals until the infants weighed over 6750 gm. and were over 6 mo. of age. The patients were then followed in the same clinic by other physicians until 1 yr. of age, when they were re-examined by the research team.

With few exceptions, all clinical examinations upon which this study is based were performed by the same individual. All laboratory determinations were performed by the same personnel throughout the study.

All infants were weighed to the nearest 10 gm. The crown-heel length of the supine infant was measured with an "Infantometer." A superficial incision in the heel provided free-flowing blood for the determination of RBC count, Hgb. and serum protein concentrations. Hemoglobin was spectrophotometrically‡ measured as oxyhemoglobin. Serum protein concentration was determined by the method described by Kagan.[4]

The differences between the means of the length gain, RBC count, Hgb. and serum protein concentrations of the corresponding birth weight groups were compared by analysis of variance (2-way classification) as described by Snedecor.[5] In the case of weight gain, the regression within each group of weight gain on birth weight was not significant, and the group averages as a whole were compared by the modified "t" test of Cochran and Cox.[6]

Results

It was found that a plot of the body weight of the infant against age generally gave a smooth sigmoid curve. The central portion of the "S" formed a remarkably straight line. The linear portion of the curve was located in the interval between 2500 and 4500 gm. body weight. This location was relatively unaffected by either age or birth weight. The slope of this linear portion was therefore taken as the measure of weight gain. The linear portion of the curve was also the period of most rapid weight gain, and it might therefore be expected to be the most sensitive to dietary changes. The slope was calculated by fitting a straight line to the data by the method of least squares.

The weight gain per week for the breast-fed group (300 gm.) was greater than the weight gain per week for either the experimental group (231 gm.) or the control group (250 gm.). The difference between the weight gains of the breast-fed and the experi-

* The olac®, polyvitamin dispersion® and oleum percomorphum were generously supplied by the Mead Johnson & Company.

† The strained meats were generously supplied by Swift & Company.

‡ The spectrophotometer was standardized for this study by the Department of Hematologic Research through the courtesy of the Director, Dr. Karl Singer.

mental group (probability <0.01) was significant whereas the difference between the breast-fed group and the control group (probability >0.05) was not significant. The difference between the weight gain per week of the experimental and control groups was also not significant ($P > 0.05$). It is not possible at this time to offer proof for any satisfying explanation for the greater weight gain of the breast-fed group.

A plot of the crown-heel length against age resulted in a sigmoid curve that paralleled the weight curve. The linear portion of the length graph was located in the same body weight interval as was that of the weight graph and showed the same relative independence of the birth weight and age. Therefore, the slope of the length graph in the interval 2500 to 4500 gm. body weight was taken as the measure of length gain. This slope also was estimated by fitting a straight line to the data by the method of least squares.

Although infants in the breast-fed group showed slightly greater length gain per week, the growth in length did not differ significantly ($P > 0.05$) between any of the groups. The actual mean length gain per week for the breast-fed group was 0.94 cm.; for the experimental group 0.89 cm.; and for the control group 0.86 cm.

The hemoglobin concentrations and red blood cell counts were each plotted against age. Inspection showed minimum values for both red blood cell count and hemoglobin at 12 weeks of age and that the values then rose steadily until about 20 weeks of age, at which time they became relatively stable. The two ages, 12 and 20 weeks, were therefore taken as critical points for comparison of hemoglobin concentrations and red blood cell counts.

There was no significant difference in the hemoglobin concentration or red blood cell count between the three groups at 12 weeks of age. At 20 weeks, however, the hemoglobin concentration of the experimental group exceeded that for the control group. The mean difference was 1.0 gm./100 cc. This difference is statistically significant ($P < 0.05$). It is of interest particularly since both groups received added iron in amounts considered more than adequate to supply the need for this mineral. At 20 weeks, the hemoglobin concentration for the experimental group exceeded that for the breast-fed group by 0.2 gm./100 cc. This difference is not significant ($P > 0.05$). At 20 weeks, the hemoglobin concentration for the breast-fed group exceeded that for the control group by an amount (0.7 gm./100 cc.) which is not significant. The lack of significance in the difference between the breast-fed and control groups is probably due to the relatively small number of observations in the breast-fed group at 20 weeks of age (14 observations in the breast-fed group; 44 in the control; 74 in the experimental). The data suggest that meat may contain some hemoglobin-producing substance which is not present in the cows' milk formula even when adequate iron is provided. It appears to be a problem worthy of further study.

There was no significant difference in the red blood cell counts between the three groups at 20 weeks of age. A fall in color index is usually observed after 3 months of age.[7] The hemoglobin, therefore, might be expected to rise first since it shows the greater deficiency.

The data for serum protein concentrations were grouped and graphed in the same manner as the hemoglobin concentrations and red blood cell counts. A gradual rise in serum protein concentration was noted with increasing age. The values at 12 and 20 weeks of age were arbitrarily selected for analysis.

The serum protein concentration was lower for the breast-fed group than for the other two groups at both 12 and 20 weeks of age. The difference was significant, however, only when the values for the breast-fed group were compared with the experimental group at 12 weeks of age (average difference 0.4 gm./100 cc.; $P < 0.01$). The lower

serum protein concentration in the breast-fed infants is of particular interest inasmuch as they showed better gain in both weight and length. At 20 weeks, the mean difference (0.35 gm./100 cc.) in serum protein concentration between the breast-fed and the experimental groups is essentially the same as that at 12 weeks. However, because of relatively few determinations at the 20 week age for the breast-fed group (14) as compared to the experimental (57) and the control (32), the difference is not significant.

In view of the higher caloric content of the meat-supplemented formula, the absence of beneficial effect on growth in weight and length suggested either poor utilization of the meat or decreased volume intake. Other studies have shown that meat is well assimilated and utilized.[2, 3]

Volume intakes for a narrow range of body weight (3000 to 3500 gm. body weight) were therefore analyzed. Data were obtained for this purpose from 41 infants in the experimental group and 30 in the control group. The average volume of daily formula intake for the experimental group was 23.0 ounces (range 12 to 30) and for the control group 28.7 ounces (range 18 to 60). The average intake in calories/kg. body weight for the experimental group was 170 (range 87 to 239) and for the control group 168 (range 103 to 326). These data were analyzed by the modified "t" test.[6] They show that the intake of the meat-fed group was significantly reduced ($P < 0.01$) in proportion to the greater caloric content of the meat-containing formula. The result was that the daily caloric intake was the same in both the experimental and the control groups. It appears, therefore, that reduction in volume of formula consumption accounts for the failure to benefit from the added calories of the meat supplement.

The mean values at one year of age were compared by analysis of variance without regard to birth weight. No differences were noted between the experimental group and the control group as a result of the difference in feeding regime during the first six months of life. There were too few of the breast-fed group available at one year of age for a satisfactory comparison.

Clinical Observations

The complaints and pertinent clinical findings were grouped and studied. The several groups did not differ significantly in the proportion of patients afflicted with constipation, irritated buttocks, upper respiratory infections, pneumonia, and diarrhea without evidence of other disease.

In the experimental group, 3 of the 59 cases of upper respiratory infection were accompanied by diarrhea severe enough to require therapy. In the control group, 6 of 41 cases with upper respiratory infection also had such diarrhea. In the breast-fed group, none of the 13 cases of upper respiratory infection were accompanied by diarrhea. The differences in the proportion of cases of upper respiratory infection which were accompanied by diarrhea are not significant. There was, therefore, no susceptibility to parenteral diarrhea which could be related to the difference in the diets.

The meat-supplemented formula was offered to 85 infants. In five it was considered advisable to discontinue the meat. One mother reported diarrhea when meat was included in the formula and constipation when it was omitted. This was observed subsequently two additional times when meat was added to the formula of this infant. Each time when meat was discontinued the diarrhea subsided. This occurred twice when the baby was given veal and once when the baby was given beef. A few months later, the infant tolerated all varieties of meat without difficulty.

Another infant developed loose and watery stools when beef was added to the formula. This also cleared when meat was discontinued. In three other infants a tendency to diarrhea, with accompanying irritability, was associated with the addition of meat to the formula. In these cases, however, the association was not as definite nor as well corroborated.

Summary and Conclusions

This study was undertaken to determine the effect on prematurely born infants of the feeding of strained meat. One group of infants received a standard formula; another an identical formula to which strained meat was added, and a third group was breast fed.

Meat added to the diet of prematurely born infants weighing between 2000 and 6750 gm. was well accepted. There was no significant difference in the symptoms or signs of illness among the infants of either of the three groups.

It was found that a plot of the body weight of such infants against age generally gives a smooth sigmoid curve. The central portion of the "S" forms a remarkably straight line. The linear portion of the curve is located in the interval between 2500 and 4500 gm. body weight. The location is relatively unaffected by either age or birth weight. The slope of this linear portion was taken as the measure of the weight gain. A similar relationship was found for the crown-heel length. These findings are not only of academic interest but are also of practical importance since they provide an unusually good tool for further nutritional and other studies.

Growth as measured by rate of change of weight and length did not differ significantly between the experimental group and the control group. The breast-fed group exceeded the experimental and control groups in both weight and length gain. The greater weight gain in the breast-fed group as compared to the experimental group was statistically significant.

Minimum values for red blood cell count and hemoglobin were observed at 12 weeks of age. These values rose steadily until about 20 weeks of age, at which time they became relatively stable. There was no significant difference in the hemoglobin concentration or red blood cell count between the three groups at 12 weeks of age. At 20 weeks, however, the meat-fed or experimental group exceeded the control by a significant amount. The mean difference in hemoglobin concentration of the experimental group and that of the control group was 1.0 gm./100 cc. This finding is of interest especially since the experimental and control groups both received more than adequate amounts of iron added to the diet.

A gradual rise in serum protein concentration was noted with increasing age. At 12 weeks of age, the serum protein concentration for the breast-fed group was significantly lower than that for the experimental group, the average difference being 0.40 gm./100 cc. The average difference between these two groups at 20 weeks was 0.35 gm./100 cc. but there were too few in the breast-fed group at this time to give the difference statistical significance. The serum protein concentrations in the experimental and the control groups did not differ significantly at either 12 or 20 weeks of age.

Analysis of the total volume intake of the formulae showed that intake of the experimental group was reduced in proportion to the greater caloric content of the meat-containing formula. The result was that the daily intake of calories was the same in both the experimental group and the control group. This remarkable reduction in volume of intake by premature infants in the weight groups concerned and the strikingly uniform caloric intake are of interest particularly in view of current thoughts on self selection of diet.

No differences were noted in the weight or length gain, hemoglobin, red blood cell count, or serum protein concentration between the experimental group and the control group when the infants reached one year of age.

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Spanish Abstract

Efectos de la Alimentacion Temprana de Carne Colada a Niños Prematuros

Este trabajo se realizó tratando de determinar el efecto que en niños prematuros podría tener la alimentación con carne colada, teniendo en cuenta publicaciones previas que habían reportado, que en el niño a término, la adición de este alimento promueve la formación de hemoglobina y eritrocitos y mejora el estado general. Un grupo de pacientes recibió una fórmula tipo; a otro le fué proporcionado una fórmula idéntica pero a la cual se había agregado carne colada, y un tercer grupo estuvo alimentado al pecho. El estudio se verificó entre julio de 1948 y mayo de 1950, y en el se incluyeron 144 niños que fueron controlados en una clínica para prematuros y que habían sido dados de alta del servicio de prematuros del Hospital Sarah Morris, por presentar un peso alrededor de 2 kilos. Se siguió una distribución igual respecto a sexo y raza y se excluyeron aquellos pacientes que no se habían vigilado periódicamente, los que se habían desviado de la dieta prescrita y aquellos que presentaron alguna enfermedad capaz de afectar su progreso.

Mientras que la fórmula del grupo control proporcionaba .95 gramos de proteínas por onza, la del grupo experimental, alimentado con carne, tenía 1.7 gramos también por onza. La relación calórica entre los dos tipos de alimento era de 19 calorías por onza para el grupo control y de 24 para el experimental. Todos ellos recibieron suplementos vitamínicos, hierro y alimentos sólidos en cantidades similares. Se veriricaron observaciones con intervalo de dos semanas hasta que el peso fué superior a 6.750 grms. y la edad a 6 meses, siendo re-examinados al año de edad.

Se hizo una comparación estadística en los 3 grupos con respecto al crecimiento, número de eritrocitos, concentración de hemaglobina y cifras de proteínas plasmáticas.

El aumento de peso por semana del grupo alimentado al pecho (300 grms.) fué mayor que el del grupo experimental (231 grms.) y que el de control (250 grms.) sin embargo, desde el punto de vista estadístico solamente la diferencia entre el grupo al pecho y el experimental, tuvo significación, mientras que tal cosa no sucedió entre los alimentados al pecho y aquellos que sirvieron como control. Tampoco tuvo importancia, valorado estadísticamente, la diferencia entre los grupos experimentales y de control.

Los niños alimentados al pecho mostraron mayor aumento de tamaño, comparativamente con los otros niños, sin embargo esta diferencia no tuvo significación estadística.

A las 12 semanas de edad no se encontró que hubiera en ninguno de los grupos variaciones importantes respecto a la concentración de hemoglobina o al número de eritrocitos. Sin embargo, a las 20 semanas, la concentración de hemoglobina del grupo experimental excedió considerablemente a la del control. El grupo alimentado al pecho tenía también una cifra de hemoglobina promedio mayor que la del grupo control, pero en este caso la variación no fué de significación estadística. Dichos resultados son de particular interés en vista de que se proporcionó hierro en cantidades teóricamente adecuadas y sugieren que la carne contenga alguna substancia productora de hemoglobina la cual no se encuentra en la fórmula con leche de vaca administrada.

A las 20 semanas de edad no hubo variaciones importantes con relación al número de eritrocitos.

Con el aumento en edad hubo una alza progresiva de las proteínas del plasma. A las 12 semanas ellas eran en el grupo alimentado al pecho, claramente mas bajas que en el grupo experimental, siendo la diferencia promedio de 0.40 grms. por 100 c.c. A las 20 semanas la diferencia entre estos mismos dos grupos era de 0.35 grms. por 100 c.c., pero el número de niños alimentados al pecho fué, en esta edad, demasiado reducido y no se puede conferir un valor estadístico a dicha diferencia. La concentración de proteínas plasmáticas en los grupos experimentales y de control no difirió en forma importante a las 12 ni a las 20 semanas de edad. Las cifras de proteínas bajas demostradas en el niño alimentado al pecho, ofrecen particular interés en vista del mayor progreso en peso y estatura de estos pacientes.

El análisis del volumen total de fórmula in gerida reveló, que en el grupo experimental, la ingestión estaba reducida en proporción al mayor contenido calórico de la fórmula, resultando que la cantidad de calorías recibidas por el grupo experimental y por el de control era el mismo. Esta reducción notable en cuanto al volumen de fórmula aceptado por los prematuros estudiados y la uniformidad de la ingestión calórica, merece gran atención teniendo en cuenta las corrientes actuales respecto a la auto-selección en la dieta.

Respecto a las observaciones clínicas, no hubo diferencias importantes en lo referente a ciertos padecimientos tales como estreñimiento, infecciones de vias respiratorias superiores, neumonía y diarrea.

Al año de edad no pudo encontrarse ninguna clara variación respecto al peso o estatura, concentración de hemoglobina, número de eritrocitos, o cifras de proteínas del plasma.

29th and Ellis Avenue

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

IT IS axiomatic to say that recent achievements in medical science have greatly improved the quality of medical care. One of the fields of study, constituting an important area of activity in which progress can be cited, is the care of the prematurely born infant. Not only has there been general utilization of new drugs and equipment, but a better knowledge and application of methods employed in reduction of the hazards confronted by the infant during this critical age period. Perhaps the most important single factor destined to influence favorably the morbidity and mortality statistics of prematures is the proper training of professional personnel assigned to their care.

During recent years many changes have developed both in the character and the content of medical education. There is little value in planning for more and better health services unless consideration is first given to providing well-trained physicians to render those services. Assumption of responsibility, with the application of fundamental principles to specific cases, is the foundation of good medical judgment. The service rendered in their local communities by practicing physicians can be only so good as the training, skills and abilities of the individuals who give it. An encouraging trend since World War II has been the very widespread effort on the part of pediatricians to avail themselves of additional training in medical centers, to acquire there the skills and modern methods so necessary for utilization in their own practice. There is general recognition of the principle that better preparation for the care of sick children and the health supervision of well children will necessarily be reflected in improved standards of practice—a step along the way toward our Academy goal of better health for more children.

Although premature babies make up only about five in one hundred of the total live births, they contribute almost 40% of the deaths in babies under one year of age. In this connection, many medical centers and teaching institutions throughout this country have arranged special short-term courses of instruction for pediatricians and nurses, giving freely of their talents to intensify the fight against premature infant mortality. Knowledge gained by participants in these courses is carried back home and applied to the improvement of existing facilities and methods there. This is a practical illustration of decentralization, without affecting adversely the services and training at the source.

It was my privilege last year to attend an institute for the care of premature infants at New York Hospital (Cornell University Medical Center.). There are similar courses of instruction located in other sections of the country, designed to meet the needs of physicians and nurses especially interested in the problems presented in premature infant care programs, either in nurseries or at premature centres. Since my personal experience is limited to the institute at Cornell, some observations concerning that particular program seem appropriate.

Sponsored and largely financed by the New York State Department of Health and the U. S. Children's Bureau, the institute affords the facilities of an outstanding medical center, and the teaching talents of recognized leaders in nursing and pediatrics, many of whom are members of the American Academy of Pediatrics. Consisting of lectures, clinical discussions and demonstrations, the curriculum includes subjects pertaining to every aspect of premature care. Field trips to similar facilities in other hospitals of Greater New York, and an opportunity for home visiting with a public health nurse, afford the student a comparison of accepted procedures. It is a stimulating experience which makes one aware that there remain many unsolved problems in this field of medicine. An attitude of friendly interest on the part of the faculty and a spirit of easy, informal camaraderie among the students add much to the effectiveness of the program. Most of the lectures and demonstrations are given jointly to physicians and nurses during the first two weeks, but the latter two weeks of the institute for nurses is devoted primarily to experience in the premature nursery with planned observations in the clinics. The instruction is intensive and highly individualized. Inquiries concerning further details may be addressed to Dr. William E. Laupus, Institute in the Care of Premature Infants, Department of Pediatrics, The New York Hospital, 525 East 68th Street, New York 21, New York.

To the busy pediatrician, engaged in private practice and conscious daily of deficiencies in his knowledge of modern methods and techniques in the handling of infants born too soon, this type of intensive postgraduate instruction is valuable. Expansion of these educational services throughout the country will inevitably result in an improvement of the type of highly specialized care so necessary for the fragile premature infant.

WARREN W. QUILLIAN, M.D., *President*

Round Table Discussion

METABOLIC DISEASES IN CHILDREN

VICTOR A. NAJJAR, M.D., Baltimore, *Chairman;* IRVINE MCQUARRIE, M.D., Minneapolis; L. EMMETT HOLT, JR., M.D., New York City; LYTT I. GARDNER, M.D., Baltimore

RUTH BAKWIN, M.D., New York City, and ERNEST L. NOONE, M.D., Drexel Hill, Pa., *Secretaries*

(Reading of Chairman Najjar's paper.)

Chairman Najjar: I have indicated to you that the alpha cells of the pancreas excrete the hyperglycemic factor. The practical value of this finding can only be measured by its possible bearing on the understanding and treatment of aberrations of carbohydrate metabolism. Dr. Irvine McQuarrie has lately found cases of hypoglycemia that showed absence of these cells. This finding is of great significance in future therapy of this condition. What may have taken years to recognize is now an accomplished fact. This we owe to the keen efforts and observations of Dr. McQuarrie who will now address us.

Dr. Irvine McQuarrie, Minneapolis: Dr. Najjar has covered the fundamental aspects of the interrelationships between hormones and enzymes involved in carbohydrate metabolism so thoroughly that I shall not need to comment on that phase of the subject in my discussion of the hypoglycemosis (hypoglycemic state), but will lean heavily upon our clinical and pathologic observations.

Spontaneously occurring, persistent hypoglycemia of severe grade with such manifestations as repeated convulsions and attacks of coma, which may be followed by irreversible damage to the central nervous system if inadequately treated, is, fortunately, a comparatively uncommon disorder. On the other hand, milder forms of the condition, characterized by such symptoms as a vague sensation of hunger or gauntness, a feeling of faintness or weakness, cold sweats and other vasomotor reactions, tremulousness, dizziness, mental confusion, drowsiness and occasional convulsions, occur with far greater frequency than most physicians appreciate. It has been estimated by several authorities on the subject that the total number of persons in the United States who are afflicted with the syndrome is almost as great as the number known to suffer from diabetes mellitus.

The complexity of the problems of etiology, classification, diagnosis and treatment of spontaneous hypoglycemia is illustrated by the schema presented in the first slide. The concept of the blood sugar concentration being dependent upon a balance between the functional activity of the insulin-producing system on the one hand and the combined activities of a series of hyperglycemia or anti-insulin factors on the other is expressed through the symbol of an old-fashioned steelyard provided with a modern pointer and scale. According to this concept, every case of spontaneous hypoglycemia is due to either absolute or relative hyperinsulinism.

The expression, "true, or absolute hyperinsulinism," obviously implies therapeutic insulin overdosage or overproduction of insulin by the beta cells of the pancreas. While it is conceivable that normally appearing insular beta cells might produce excessive amounts of insulin at times in response to nervous or other extrapancreatic stimuli, the evidence that this is an important cause of spontaneous hypoglycemia in any but the mildest cases is not entirely convincing. Tumors (adenoma and carcinoma) and hyperplasia, involving the beta cells of the pancreatic islands, constitute the only satisfactorily demonstrated pathologic lesions associated with absolute hyperinsulinism. Successful surgical excision of a benign islet tumor results in complete cure of the hypoglycemosis. Such tumors are extremely rare in children. Subtotal pancreatectomy in cases showing islet hyperplasia is frequently highly beneficial, at least temporarily.

Alloxan used by Talbot and coworkers as a last resort in one severe case of hyperinsulinism appeared to give satisfactory results. Because of its marked hepatotoxic and nephrotoxic action, this agent should obviously be used with extreme care if used at all.

The term "relative hyperinsulinism" refers to the state in which hypoglycemia results from

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underactivity of one or more of the nervous, hormonal, nutritional or other antagonistic factors lined up in our schema on the side of the balance opposite that occupied by the symbolic pancreas. Hypocorticoadrenalism (Addison's disease), anterior pituitary deficiency (Simmonds' disease and certain cases of pituitary dwarfism), extensive liver disease (necrosis, atrophy, acute hepatitis, cirrhosis and von Gierke's glycogen storage disease) are the most commonly recognized disease entities causing relative hyperinsulinism. In all these clinical conditions the hypoglycemia is characterized by its appearance almost exclusively at times most remote from meals, indicating a deficiency in the glycogen stores of the liver or a deficiency in the mechanism for breakdown of glycogen to glucose (glycogenolysis), as in von Gierke's disease. The net clinical significance of deficiencies in the cellular activity of the thyroid, posterior pituitary, adrenal medulla, islets of Langerhans (alpha cells) and ovaries and of disturbances in the functions of the sympathetic and parasympathetic nuclei in the hypothalamus, as regards the production of hypoglycemia, cannot be accurately appraised at the present time. Perhaps future investigations on these aspects of the problem will shed new light on the pathogenesis of so-called idiopathic hypoglycemia, which constitutes the largest single group of hypoglycemia children in our experience.

As regards treatment of the etiologically different types of spontaneous hypoglycemosis, nothing further needs to be said concerning true hyperinsulinism. Obviously, for those patients who suffer from adrenocortical insufficiency or pituitary insufficiency, specific replacement therapy and avoidance of fasting are indicated. The most important feature of the therapy for hypoglycemia due to the various forms of liver disease already referred to is that which is directed to the primary disease itself. In the milder forms of so-called functional hypoglycemia, the etiology of which is more or less obscure, the most satisfactory form of treatment is that involving the use of the high-protein, comparatively low-carbohydrate diet recommended by Conn.

Shortly after it was announced by Corey and Britton and by Long in 1939 that adrenal cortical extract in excessive dosage exerts a diabetogenic effect in normal animals, we attempted to exploit the discovery by administering comparatively large doses of commercially available extracts to young children suffering from severe spontaneous hypoglycemia of non-Addisonian type. While the results in a few instances were mildly encouraging, they were not sufficiently definitive to justify the expense entailed in routine use of the extract.

On the basis of the well-known observation by Young and by others, that continued administration of crude extracts of the anterior lobe of the pituitary gland produces glycosuria and hyperglycemia (diabetogenic effect) in normal experimental animals, we treated a young hypoglycemic pituitary dwarf with large doses of one of the then available commercial extracts of this gland (polyansyn®, Armour) in 1940. The patient had had generalized convulsions on several occasions while his fasting blood sugar was in the neighborhood of 20 mg. %. Morning convulsions ceased to occur and his fasting blood sugar subsequently was found to be within normal range. A recent check on the patient's progress revealed that convulsions have never recurred.

When adrenocorticotropic hormone (acthar®) was found by Brown (1943) and by Conn (1948) to induce hyperglycemia and glycosuria in normal men, it became apparent to us that its effects on spontaneous hypoglycemia should be studied.

Metabolic data on 12 non-Addisonian hypoglycemia patients included in our study of the problem indicate that their responses to ACTH administration are similar in type to those reported for normal adult subjects. Severe hypoglycemia and attendant symptoms were completely abolished during the period of intensive hormone administration and usually for a few days after its withdrawal. The sharp fall and the abnormally prolonged, low level of blood sugar in the glucose-tolerance curve, which represented the characteristic response of each of the patients during the control period, were found to be absent during the period of ACTH administration, the curve becoming essentially normal. The eosinophil cells of the blood fell precipitately from the normal range (between 100 and 350 cmm.) to between 0 and 10 cmm. within 4 hours after ACTH was first administered and remained at this low level so long as the hormone was given at 6 hour intervals.

As Dr. Najjar has indicated, it has been demonstrated by previous workers in experimental animals that the alpha cells of the islets of Langerhans exert an anti-insulin or hyperglycemic (glycogenolytic) effect. We have recently made metabolic and histologic studies on 2 patients suffering from spontaneous hypoglycemosis (brother and sister) in whom absence of pancreatic alpha cells appears to be the most likely etiologic factor. Special biochemical tests for dysfunction of the adrenal cortex, the adenohypophysis and the liver were negative. No evidence of adenoma or hyperplasia of the beta cells of the pancreatic islets could be found in these two patients when subtotal pancreatectomy was performed. However, examination of sections of the pancreas stained with

Gomori's special stain unexpectedly revealed the total or almost total absence of alpha cells. That the patients showing these unusual characteristics represented a heretofore unrecognized endocrinologic entity is suggested by the familial occurrence of the syndrome and the initial appearance of symptoms during the first months of life. Adrenocorticotropic hormone was found to be highly effective in control of the hypoglycemia. In fact, this new hormone appeared to be as effective for the control of all cases of non-Addisonian hypoglycemia as insulin is for the control of diabetes mellitus. Our most severe case, the younger of the 2 with absence of alpha cells, lost her tendency to spontaneous attacks of hyperglycemia after one year of ACTH therapy.

Fasting hypoglycemia and morning convulsions were prevented temporarily by ACTH therapy in one young patient with glycogen storage disease. The glycogenolytic substance derived from the pancreas did not induce hyperglycemia in this patient with von Gierke's disease.

Dr. Philip Rosenblum, Chicago: Would growth hormone be indicated for hypoglycemia in view of what Dr. Najjar has said?

Dr. McQuarrie: It inhibits carbohydrate metabolism so I would be reluctant to try it for fear it might do some harm.

Chairman Najjar: Growth hormone seems to depress glucose uptake so that one might get an overall effect of combatting hypoglycemia. However, since the effect of the hormone is not limited to carbohydrate metabolism, I would hesitate to use it as a therapeutic measure.

Dr. Francis W. Helfrick, Manchester, Conn.: Has anyone had experience with ACTH in the glycogen storage disease of muscle, distinct from that of the liver type?

Chairman Najjar: I do not know of any published work on the effect of ACTH on liver glycogen as contrasted to its effect on muscle glycogen disease.

Dr. Holt has been interested in glycogen disease for quite some time. I am sure we will all welcome Dr. Holt's comments on this subject.

HEPATIC FORM OF GLYCOGEN DISEASE (VON GIERKE'S DISEASE)

Dr. L. Emmett Holt, Jr., New York City: My remarks will be confined to the hepatic form of glycogen disease (von Gierke's disease), the only one in which I have had any experience. A few years ago Dr. Edward Bridge and I reported upon this disease. We made some clinical observations, noting among other things a tendency to obesity and a favorable response to indirect carbohydrate therapy (e.g., extra protein therapy). We also attempted to throw light on the nature of the glycogenolytic defect. I shall now report some experiences and further observations made in the interim which have in part confirmed and in part changed the points of view we held at that time.

I am inclined to think that Dr. Bridge and I were unduly rigid in demanding that the liver should contain 10% or more glycogen to establish the diagnosis of von Gierke's disease. I have since seen unquestionable cases in which analysis of biopsy specimens gave a lower figure. In the past glycogen disease has been regarded as an all-or-none affair; different grades of severity were not appreciated. There is, however, suggestive evidence that differences in severity exist. This evidence is partly clinical, partly chemical and partly histologic. Hypoglycemia is much more of a problem in some patients than others, and the same may be said of ketosis. The glycogen content of the liver may vary at least between the limits of 6% and 15%. In typical cases the microscopic appearance of the liver cells is characteristic—they are large "plant-like" cells—3 to 4 times the diameter of a normal liver cell, with a centrally placed nucleus and small cytoplasmic granules filled with glycogen. In appearance they resemble early embryonic hepatic cells and all the liver cells are so affected. My colleague, Dr. William Von Glahn, has called my attention to the existence of livers in which the typical appearance of von Gierke's disease is present in certain areas of the liver only, those elsewhere appearing quite normal. It is of interest in this connection that in the cardiac form of von Gierke's disease the large vacuolated embryonic type of cell commonly affects the entire heart. However, there are encountered hearts in which such changes are found only in localized areas. These cases are usually diagnosed as rhabdomyoma. Thus it is possible that both in the hepatic and cardiac forms of glycogen disease incomplete forms may exist.

Acetonuria is commonly thought to be an invariable and striking characteristic of hepatic glycogen disease. We were troubled at not finding this symptom in an otherwise typical case until the report of Van Creveld came to our attention, pointing out that acetonemia may exist without acetonuria. The suggestion has been made that when the glycogen disease affects the kidney as well as the liver, this situation may prevail. Studies of kidney function in renal glycogenosis are needed to confirm this.

Although hepatic glycogen disease is commonly thought to be a disorder of carbohydrate metabolism alone, it has been clear for some time that there is, during infancy at least, a concomitant disorder

of fat metabolism. The literature contains a number of reports of lipemia in these cases and Dr. Bridge and I, in one of our patients studied in Baltimore, observed the disappearance of this phenomenon between the age of 2 and 6 years. A second instance of such disappearance has since come to my attention. In keeping with the observations on early lipemia are analyses of the liver itself made at this period in the disease which have shown abnormal accumulations of fat together with glycogen; such findings have not been reported in older subjects.

As Dr. Najjar has pointed out, the nature of the glycogenolytic defect in this disease is still obscure—it may be that the glycogen itself is abnormal in structure or it may be that the enzyme system is faulty. Since most enzyme systems are reversible it is difficult to explain the coexistence of defective glycogenolysis with normal glycogenesis. There is, however, evidence that in one step of the process a different enzyme is concerned in the synthetic and the lytic process: the formation of glucose 6-phosphate from glucose is performed by the enzyme phosphokinase, whereas the degradation of glucose 6-phosphate to glucose is performed by glucose 6-phosphatase. This unusual relationship suggested to us that glucose 6-phosphatase might be the deficient factor in glycogen disease, since such a deficit would permit normal glycogenesis but defective glycogenolysis. Through the kindness of Dr. Spurtes in Dr. Ochoa's department measurements of glucose 6-phosphatase were made on a specimen of liver removed at biopsy from one of our patients. The quantity of this enzyme was found to be low as compared with a normal liver. We do not, however, feel justified in drawing the conclusion that glucose 6-phosphatase is defective in this disease since the size of the liver must also be taken into account. Even though the enzyme was low in terms of a unit of liver weight, the quantity present in the liver as a whole did not appear to be reduced.

I shall close by mentioning some recent clinical experiences with von Gierke's disease—some pleasant and some the contrary. On the positive side, we have had further clinical experience with an additional late evening meal, high in protein and can confirm the observation that under these conditions normal growth is resumed, the additional protein serving to make up for the protein which in this disease is diverted from growth needs to meet the needs of carbohydrate metabolism. There is also now available from several sources information indicating that some tendency to recovery from the carbohydrate metabolic defect occurs with adolesence, and it may be that complete recovery eventually occurs.

On the unpleasant side I should like to record two experiences. In one instance in which my advice was sought as to whether a further pregnancy should be undertaken in a family whose first child had died of glycogen disease, I made the error of belittling the possibility of its occurrence in siblings and was properly embarrassed when the second child exhibited the disease. When one considers the reports of glycogen disease in the literature, most have been isolated instances and only a few have been in siblings. However, when one considers the reports in which information on siblings was available, the familial incidence is impressive.

My second unpleasant experience was in the case of a child of 11 months with what appeared to be a minor upper respiratory infection who was fasted 16 hours to make observations on the blood sugar curve. The patient went into collapse, developed hyperpnea, was found to be acidotic and hypoglycemic and despite vigorous administration of intravenous glucose, the hypoglycemia was difficult to control and a fatal termination occurred within a few hours. A seond patient, in which the sequence of events was almost identical, I saw with Dr. Murray Bass, who has knowledge of several other like ones. The explanation for these untoward episodes is not altogether clear. The acidosis was not a ketone body acidosis, judged by the absence of ketonuria, but this does not exclude the possibility of ketonemia without ketonuria. Accumulation of lactic acid has been noted by H. H. Mason under such circumstances and we may have been dealing with a lactic acid acidosis. It is difficult to escape the conclusion that some defect of carbohydrate utilization is coupled with the defect of glycogenolysis. Only thus can one account for the difficulty in sustaining the blood glucose level. Resistant hypoglycemic states have been observed in other conditions—particularly in terminal diarrheas. Whatever the explanation these experiences have made us extremely cautious in carrying out any procedure that involves even very temporary withholding of food.

Dr. Harry T. Nagel, Maywood, Ill.: Has ACTH been tried in the therapy of glycogen storage disease?

Dr. Holt: We treated one of the cases in Baltimore with cortisone which was then known as compound E. There was only a small amount available, enough to treat a patient for one day. This was inadequate treatment for it failed to accomplish anything.

Dr. Samuel S. Glick, Baltimore: Have you had any experience with cases of glycogen disease involving the heart?

Dr. Holt: No.

Dr. D. Thurston, Glendale, Mo.: In what way do salicylates interfere in carbohydrate metabolism? I mean salicylate poisoning where you get hypoglycemia. The British have reported the use of salicylates given in large doses in a syndrome that is characteristic of the one due to excess cortisone.

Chairman Najjar: The effect in salicylate poisoning may well be due to excessive utilization of glucose. The increase in metabolism following high doses of salicylate may be the result of increased tissue respiration. The effect may be similar to that exerted by dinitrophenol. This substance increases the metabolic rate apparently by dissociating two well coordinated processes in metabolism, i.e., oxidation and phosphorilation. Thyroxine seems to act in such a manner. If salicylates have a similar effect, then the absorption of glucose will be interfered with and what is absorbed will be quickly oxidized, eventually producing hypoglycemia.

Dr. H. B. Rothbart, Detroit: Dr. Holt, do these defects right themselves after the age of puberty?

Dr. Holt: Yes, as far as I know.

Chairman Najjar: In connection with this question I would like to stress the possible multiplicity of defects in this disease. As I mentioned earlier, the glycogen in one case tested by Dr. G. Cori was abnormal. That case had cirrhotic changes in the liver. On the other hand, similar cases were also studied and showed a normal type of glycogen. This then is definitely not the only defect one might encounter in glycogen disease. When an organ like the liver can synthesize glycogen, it necessarily means that all the enzymes needed for synthesis are present. With the exception of the first enzyme, hexokinase, all the others are reversible down to the glucose-6-phosphatase step. This step is the most logical one to incriminate, in that the enzyme would be absent in glycogen disease of the liver. If that is true, this type of defect can apply only to glycogen disease of the liver, since normal muscle has no such enzyme and therefore cannot produce glucose from its glycogen stores. Glycogen disease of muscle would be caused by some other type of defect.

Dr. Nelson Newmark, Springfield, Mass.: How often do you do a liver biopsy or muscle biopsy for diagnosis?

Chairman Najjar: If there is a large liver with symptoms of hypoglycemia, one is fully justified, I believe, in suspecting glycogen disease and for verification a liver biopsy would be indicated. Regarding muscle biopsy, the problem is a little different. Cases with glycogen disease of muscle alone show little or no demonstrable disturbance in carbohydrate metabolism. The only clue they offer is enlargement of the heart and cardiac failure. Under these circumstances, when no common disease of the heart is suggested by the course of the illness, then one is justified in obtaining a piece of skeletal muscle for study.

Dr. Carl Zelson, New York City: Did you find an increase in urinary amylase with a decrease in blood amylase?

Dr. Holt: Amylase was not studied.

Dr. Carl Zelson, New York City: In my case we had a definite decrease in blood amylase with a marked increase in urinary amylase.

Dr. Holt: We tried amylase in vitro; the glycogen was split down. We tried treating a child with amylase without any effect at all.

Dr. Hyman Alford, Newton, Mass.: Are there any characteristic ECG changes?

Dr. Holt: There have been ECG changes reported but I wouldn't say they are characteristic.

Chairman Najjar: Before proceeding with another aspect of this problem which Dr. Lytt Gardner will discuss, I would like to comment on the question that Dr. Holt raised regarding the irreversible hypoglycemia observed by him and leading to death. It is fortunate that such cases are in the minority. Most cases of glycogen disease do not show such severe hypoglycemia. The irreversible damage may well be due to the fact that brain tissue that derives its nutrition mainly from glucose cannot under certain circumstances withstand prolonged hypoglycemia. Either that, or that the real damage is done when there is loss of potassium from the brain cell due to poor availability of glucose. It has been demonstrated that potassium moves out of the cells when glucose is withheld from brain tissue and moves back in again when glucose is furnished.

We will now hear from Dr. Lytt Gardner, who will discuss some hormonal influences on carbohydrate metabolism.

EXOGENOUS HYPERADRENOCORTICISM

Dr. Lytt I. Gardner, Baltimore: It seems appropriate at this time to review some of the metabolic effects of exogenous adrenocortical hormones on protein, carbohydrate, fat and electrolyte metabolism. These effects bear directly on the function of cellular enzymes, since enzymes are proteins which participate intimately in intermediary organic metabolism, and which require a specific ionic environment.

Such considerations are also essential to a proper understanding of the toxic effects which may result from the administration of ACTH or cortisone-like steroids.

Whereas endogenous hyperadrenocorticism of the Cushing's syndrome type is a rare disease in children, the last 2 years have seen exogenous hyperadrenocorticism due to ACTH or cortisone become a common pediatric condition. Furthermore, new adrenal steroids are on clinical trial, and it is likely that the pediatrician will soon have to cope with them. Hydrocortisone (compound F; 17-hydroxycorticosterone) has recently been administered orally to adult arthritic patients by Ward, Slocumb, Polley, Lowman and Hench with antirheumatic effects similar to those produced by cortisone. Wilkins, Gardner, Crigler, Migeon and Silverman have administered hydrocortisone to a child with congenital adrenal hyperplasia with androgen-suppressive effects equivalent to cortisone. The latter workers have also administered corticosterone (compound B) to one infant with the Na-losing type of congenital adrenal hyperplasia. There resulted an improvement in Na retention and partial suppression of the excess androgens.

In view of the increasing multiplicity of these therapeutic agents in pediatrics, let us review some of the knowledge concerning their physiologic effects.

Intermediary Metabolism of Carbohydrate, Protein and Fat

Twenty years ago Britton and Silvette at the University of Virginia discovered that the administration of adrenal extracts to normal and adrenalectomized animals produced an increase in the concentrations of blood sugar and liver glycogen. These experiments were amplified by Long, Katzin and Fry at Yale, who published their definitive study in 1940 (Endocrinol. **26**:309, 1940). These workers found that the administration of adrenal extract or crystalline 11-oxygenated steroids (cortisone, hydrocortisone and corticosterone) caused an increase in the concentrations of blood sugar and liver glycogen, and an increased urinary N excretion. Their animals showed an absolute increase in body carbohydrate and a decrease in respiratory quotient as measured by the Haldane device. Thus there appeared to be a slowing down in the oxidation of glucose, together with an increase of gluconeogenesis from protein. Later Li, Simpson and Evans found that there was an absolute increase in body fat of rats treated with ACTH. Clinical studies in man by less direct methods have borne out most of these findings. Whether there is a negative N balance in man seems to depend upon appetite, since some patients on large doses of ACTH or cortisone maintain a positive N balance in the face of excess urinary N loss by voluntarily increasing their food intake. As F. L. Engel has pointed out (Am. J. Med. **10**:556, 1951), the possibility exists that the hyperphagia which frequently accompanies ACTH or cortisone therapy represents a homeostatic response by the body to prevent undue N loss.

Electrolyte Metabolism

There is great variation among adrenal steroids in their respective influences on electrolyte and organic metabolism.* Desoxycortisosterone (DCA) is potent in causing urinary Na retention and K excretion, but it has essentially no effect on carbohydrate metabolism. Corticosterone occupies an intermediate position. It has some DCA-like effect on Na and K, and in addition has an influence on carbohydrate metabolism. At the other extreme both cortisone and hydrocortisone have relatively little Na-retaining effect, but have a very marked carbohydrate effect. In the presence of an intact adrenal cortex, ACTH is quite effective both on electrolyte and carbohydrate metabolism.

The continued administration of cortisone or ACTH may result in cumulative K deficiency. K deficient animals show myocardial lesions, electrocardiographic changes and replacement of intracellular K by Na, Mg and Ca. Serum K and Cl concentrations are low, and serum CO_2 concentration is high. In such animals chronic diarrhea may develop. The administration of K rapidly corrects the metabolic abnormalities.

Most of the above findings have been described in patients with chronic K deficit, and the administration of K parenterally or by mouth has been beneficial.

Detection and Management of Adrenal Hormone Toxicity

It should be pointed out that toxic effects are most likely to be seen in those diseases which require a therapeutic dose level of ACTH or cortisone that approaches the toxic level. Rheumatoid

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* The relationships of chemical structure to physiologic action of adrenal steroids were outlined in a previous Panel Discussion: The Adrenal Gland in Health and Disease, A. W. Jacobsen, Chairman, PEDIATRICS **3**:515, 1949.

arthritis, rheumatic heart disease and the hypersensitivity syndromes are examples of this group. On the other hand, an entirely different mode of action of cortisone appears to obtain in congenital adrenal hyperplasia, so that fortunately in that group of cases the effective dose of cortisone is usually well below the toxic level.

Some of the metabolic abnormalities previously described may serve as aids in appraising the clinical state of children on chronic therapy with ACTH or the 11-oxygenated steroids.

1. Disordered Carbohydrate Metabolism: If a diabetic child is given ACTH or cortisone for any reason, one should expect an immediate increase in insulin requirement. In nondiabetic children disturbances of carbohydrate metabolism on hormonal therapy have been rare.

2. Disordered Protein Metabolism: The maintenance of proper N balance in a growing child on chronic ACTH or cortisone therapy poses a serious problem not encountered in adult patients, since somatic growth is a sensitive reflection of N balance. Because these hormonal agents may produce negative N balance if N intake is not adequate, the pediatrician must watch carefully the appetite and food intake of such patients, especially the protein intake. In infants and children receiving ACTH or cortisone, the use of testosterone to enhance N balance is contraindicated. Periodic measurement of longitudinal growth, body weight, and bony maturation by x-ray are simple, objective procedures which aid in estimating clinical progress.

Interference with the normal formation of immune proteins may result from intensive hormonal therapy. As a result a previously positive tuberculin test may react negatively, and septicemia or parasitemia may develop silently. Interference with fibroblastic proliferation may result in abscesses of atypical architecture.

3. Disordered Electrolyte Metabolism: Fluid retention with edema is often the first sign of K deficit in patients receiving ACTH or cortisone. A daily chart of fluid intake-output is useful in predicting trouble. When such patients develop low serum Cl and increased serum CO_2 concentrations, K deficit is a virtual certainty. The finding of a low serum K concentration is confirmatory, although more difficult technically. Electrocardiographic abnormalities, such as low or inverted T-waves, depressed ST segments and prolonged QT interval may develop. If dietary Na restriction is ineffective, the addition of 0.5 to 3 gm. KCl by mouth each day may be helpful.

Summary

The administration of ACTH or 11-oxygenated steroids to animals results in: (a) increased blood sugar and liver glycogen concentrations, partially as a result of decreased glucose oxidation; (b) increased urinary N excretion; (c) increased total body fat, and (d) tendency toward Na retention and K deficit. In clinical studies these findings have been largely confirmed, using indirect technics. Children on long-term treatment with full doses of adrenal hormones present a special problem, since the foregoing metabolic abnormalities cause inhibition of somatic growth. Periodic clinical appraisal of these patients with careful longitudinal measurements, body weight and x-rays for bony maturation are suggested. The importance of a food intake adequate to offset a negative N balance is stressed, as well as the provision of added K to prevent chronic K deficiency.

Question: How soon after you start treatment does K deficiency develop? That is, if you are using cortisone.

Dr. Gardner: Compared with desoxycorticosterone, cortisone is a relatively weak K depleting agent, and the development of clinically measurable K deficiency on full doses of cortisone may take several weeks or even longer. This variability of K depleting effect may depend to a great extent upon the dietary intake of Na, since K deficit appears to develop much more readily in the presence of adequate or more than adequate Na intake.

Chairman Najjar: In bringing this discussion to an end, I would like to repeat some of the highlights presented here. We know now that some cases of hypoglycemia show absence of the alpha cells of the islet tissue of the pancreas. When pancreatic tissue is obtained under circumstances requiring surgical exploration, one must look for the alpha cells. These cells excrete a hormone, heretofore unsuspected, the hyperglycemic hormone. This is in the process of being produced commercially and should be available in the future. This hormone may well have the therapeutic potentialities for those cases, as insulin has for diabetic patients. Cases with glycogen disease may show severe and irreversible hypoglycemia. Some cases show abnormal glycogen and there is a good possibility that a defect in the enzyme system is responsible. Hormones play a significant role in carbohydrate metabolism and, when uncontrolled, may have a deleterious effect as witnessed by the development of Cushing's syndrome following ACTH therapy.

CARBOHYDRATE METABOLISM

A Symposium

CHARLES H. BEST, M.D., *Chairman*
University of Toronto Medical School, Toronto

TWO DIABETIC CHILDREN

ELLIOTT P. JOSLIN, M.D.
Boston

INFANTILE DIABETES

ALVAH L. NEWCOMB, M.D.
Winnetka, Ill.

ACTION OF INSULIN

CHARLES H. BEST, M.D.

INSULIN EXTRACTABLE FROM PANCREAS IN NON-DIABETIC AND DIABETIC CHILDREN

GERALD A. WRENSHALL, PH.D.
University of Toronto Medical School, Toronto
and
R. C. RICHIE, M.D.
Hospital for Sick Children, Toronto

MANAGEMENT OF DIABETES IN CHILDREN

A. L. CHUTE, M.D.
Hospital for Sick Children, Toronto

PROGNOSIS OF JUVENILE DIABETES

PRISCILLA WHITE, M.D.
New England Deaconess Hospital, Boston

Presented at the Annual Meeting of the American Academy of Pediatrics, Toronto, Oct. 24, 1951

TWO DIABETIC CHILDREN

ELLIOTT P. JOSLIN, M.D.

This is the second time I have had the honor of appearing before a pediatric gathering. The first was in 1917, when I spoke at the Boston Medical Library. Pessimism then was so rampant about diabetes in childhood that I asked Rexane, 4 years old, with diabetes of 2 years' duration, to come to the meeting and to dance and to sing before the doctors to show a child could be happy, though diabetic. I believe it made an impression, just as did her picture with her dog in her arms when I showed it to a Committee of the Massachusetts Legislature and pleaded with them not to outlaw attempts with animals to discover a better treament of diabetes. Her mother added to the occasion when she said she knew Rexane's dog, Tevis, would willingly give his life to save Rexane.

Rexane's father was the Admiral who laid the North Sea barrage in the first World War. In fact Tevis was with him, tumbled into the sea at Cherbourg, but was rescued by the sailors. Rexane at 5 went on the stage of the local theatre to sell Liberty Bonds so as to protect her daddy and other children's fathers and bring them home. But I suspect this was not all Rexane accomplished. Later, another Admiral, her family's friend, and our patient, developed the disease, lived successfully, and just recently, after an interval of 27 years, through his widow, left to the Harvard Medical School $185,000 for research in diabetes.

I hope you do not take it amiss that our group cares for so many diabetic children. In a way it is not our fault. It came about because that sainted pediatric professor whom we all so much respect once exclaimed he hoped he would never see another diabetic child. And so these tiny diabetic urchins came to us, largely because no one else wanted them and also because Frederick M. Allen gave us the courage to starve a child to let him live with the hope of better days in store. And to prove I was justified in so doing, I have continued to report upon all our fatal cases; an idea which I still believe sound and hope others may imitate. Rexane was 29th on my list in 1922 to get insulin, but died because we postponed entrance to the hospital until after the Christmas holidays.

The stone which the builders rejected became the head of the corner and so when we started our Expectation of Life Medal, we used the symbol of a child sailing his boat on uncharted seas.

Today our children remain our explorers of uncharted diabetic seas. So many adults have now received those medals for having lived longer with diabetes than they were expected to live without it, that sometimes one wonders if the day will come when we will cultivate diabetic patients, because they may become healthier, more rugged and perhaps have more self control, common sense and intelligence than the nondiabetic. Bouchardat recognized this a century ago. It can be accepted as a fact that medals, honorary degrees and distinctions are received by diabetic patients far out of proportion to their number in the population. Who knows what the future holds? It may be a distinction to have a diabetic ancestor in a branch of your family tree. Don't we need diabetic patients to teach us how to postpone arteriosclerosis?

Today "seeing is believing" and so I have asked one of our children to fly to Toronto. He developed diabetes at 14 years of age in 1920, began treatment at the Columbia Medical Center that same year, and the next year started the use of insulin. He fell to my lot because someone in my family had the foresight to marry his aunt.

His diet in the first few years was always meagre: carbohydrate 50, protein 90 and fat 75 gm., but he held to it. At that time, perhaps my best diabetic nurse entered his family. In 1922, with 3% glycosuria and 3+ diacetic acid, he fasted and became sugar-free. Slowly his diet was raised at first to carbohydrate 27, protein 38, fat 99 gm. and subsequently, carbohydrate 56, protein 64, fat 150 in 1927 and since then the diet has risen gradually to at least carbohydrate 180, protein 90 while fat has dropped to 100 gm.

His nurse cared for him 7 years here and abroad, taught him how insulin could be lessened when he played tennis hard in the Bois de Boulogne, and how he and she alone could safely fly his aeroplane on week end trips from New Jersey to Cape Cod. Since his marriage, his wife and he have devoted themselves to controlling his diabetes day in and day out, bringing up a family of 3 children, and he has conducted without interruption by sickness, related to diabetes, an extensive business.

This patient, Case No. 2410, whom you now see, is our first Quarter Century Victory Medal Case, receiving the medal in 1946 because of perfect eyes, perfect arteries and a sound body, all certified by specialists. To encourage you and me, he and his wife are paying us the honor of flying some thousand miles to prove what St. Paul once said: "That he that ploweth, should plow in hope and that he that thresheth in hope should be partaker of his hope."

INFANTILE DIABETES

ALVAH L. NEWCOMB, M.D.

Dr. Best has paid me an undeserved compliment for arranging this excellent program. I had no part in it except to suggest to Dr. Silverthorne that a program on carbohydrate metabolism was mandatory when we met in Toronto, the city of Banting, Best and insulin.

Dr. Wrenshall's work on the assay of extractable insulin from the human pancreas is another milestone in the advance of medicine. It is hoped that the next step will be a method for the assay of the circulating insulin.

We are going to discuss the symptoms and signs of diabetes mellitus which we observed in 6 infants at the Children's Memorial Hospital. These 6 patients were discovered during the admission of 202 diabetic children.

The clinical picture and the difficulties in making a correct initial diagnosis of diabetes in acutely ill infants with infection will be presented. Dr. Alexis F. Hartmann, at a seminar on Sunday, suggested that an admitting resident or nurse with a keen sense for the odor of acetone ought to establish the diagnosis at once. Certainly, a diagnosis of diabetic acidosis ought soon be established by the detection of glycosuria and ketonuria, if one suspected that syndrome on hospital admission.

The symptoms and signs in our 6 patients in order of frequency are listed below. It will be noted that polyuria and loss of weight are the only cardinal symptoms of diabetes presented:

Fever	100%
Pulmonary signs and symptoms	100%
Accelerated respiration	100%
Rales and signs of pneumonia	66%
Anorexia and vomiting	66%
Restlessness	66%
Polyuria	66%
Loss of weight	33%

The predominance of symptoms and signs of severe respiratory infection in infants with diabetes is not given prominence in the world's literature. We wish to point out the possibility of diabetes in infants as one disease to eliminate in the differential diagnosis when severe respiratory symptoms and signs improve with replacement fluid and electrolyte therapy and the antibiotics, but when hyperpnea persists.

The following case report indicates an extremely severe type of the disease. J. G., a 12 month old baby boy, patient of Doctor Arthur Shafton, was admitted to the Children's Memorial Hospital, with a history of restlessness, anorexia for 3 days and a fever of 38.3°C. The day prior to admission, he vomited twice and the respirations became heavy and rapid. The following morning, after vomiting twice, he was rushed to the hospital.

Birth, developmental and family histories were noncontributory.

Physical examination revealed a well-developed comatose infant boy in shock and not responding to stimuli. The temperature was 39.4°C. rectally and the respirations were 42/min., being deep and regular with flaring of the ala nasae. The pulse, thready and weak in quality, was 136/min. Fine rales were heard at both bases with suppression of the breath sounds at the right base. Bronchial breathing was heard in the left axilla. He was treated for pneumonia immediately with penicillin and plasma and 250 cc. of one-sixth molar sodium lactate given intravenously. Supportive measures initially produced a good response. Within 6 hours after admission, the chest had cleared remarkably with only a few rales remaining; however, the respirations remained deep and rapid and the patient was still comatose. A urinalysis revealed 4+ sugar, acetone and diacetic acid. The carbon dioxide content was 15.5 vol. % and plasma chlorides were 373 mg./cc. Twenty units of regular insulin were given subcutaneously. The same dose was repeated in 3 hr. After 6 hr., 10 units were administered. At that time, the urine showed 2+ sugar, 4+ acetone and diacetic acid. A total of 300 cc. of normal saline, followed by 400 cc. of 5% dextrose in water were given intravenously.

Fifteen hours following admission, the urine showed 3+ sugar and 4+ acetone and diacetic acid. Ten units of regular insulin were then given. Response was noted shortly and the patient awakened. The urine was only 1+ with 3+ acetone and diacetic acid. Four units of regular insulin were given 3 hours after the last injection. Three hours later, 21 hours after admission, the patient developed

severe, near fatal, insulin shock with apnea and cyanosis. He was revived by artificial respiration and rapid intravenous injection of 10% dextrose in water.

He was then placed upon a 6 hour management with intravenous feedings until he was able to eat, which was on the fourth hospital day.

The correct admission diagnosis was made in only one of the 6 patients. Acidosis, renal anomaly and acidosis, bronchopneumonia, meningitis and bronchopneumonia, and shock were listed as the clinical impression on admission to the hospital.

ACTION OF INSULIN

CHARLES H. BEST, M.D.

The subject of the action of insulin has interested hundreds of scientists since Banting and Best asked themselves this question in 1921. The junior partner wrote his M.A. thesis in physiology in 1922 on the changes in respiratory exchange produced in diabetic dogs and a diabetic patient (the first doctor to be treated with insulin, who lived until a few months ago). Everyone agrees that insulin accelerates the removal of glucose from blood and its entry into tissue cells where it is formed into fat and glycogen. Insulin removes the blocks in enzyme action necessary (1) for the formation of glucose-6-phosphate or its conversion to fructose-6-phosphate, and (2) the synthesis of fatty acids from 2 carbon compounds. The fall in blood phosphate and potassium are related to these intracellular conversions but the steps are not yet clear. The interaction of insulin and the growth hormone and their combined and individual effects on nitrogen balance and protein synthesis were discussed. Dr. Best was convinced that the evidence in human subjects (Bondy, Sherlock) showed that insulin decreased gluconeogenesis from protein. This is another anabolic effect. The recent work with labelled dextrose strongly indicates that combustion of glucose is also increased by insulin and it appears probable that older conceptions to the contrary will have to be revised unless the isotopes are leading us astray. The group of catabolic processes, collectively called diabetes mellitus, are converted by insulin to anabolic reactions at the expense, apparently, of the combustion of a part of the sugar which disappears.

INSULIN EXTRACTABLE FROM PANCREAS IN NON-DIABETIC AND DIABETIC CHILDREN

GERALD A. WRENSHAW, PH.D., *and* R. C. RITCHIE, M.D.

The insulin extractable from pancreas (I) has been determined by a standardized procedure in a series of 84 nondiabetic and diabetic children.

In the nondiabetic subjects no trend was observed between the concentration of I and interval between death and autopsy. The concentrations of extractable insulin in islet tissue and in the beta-cells have been estimated. The former increases with age. The latter amounts to about 1% of the estimated wet weight of beta-cell tissue. The concentration of I decreases slowly with age. On the other hand I increases with age from prematurity through birth, a maximum being reached at about 6 months after birth followed by a shallow minimum occurring in the third year of life. I rises continuously thereafter, reaching adult level between the twelfth and seventeenth years of life. During this time, no sex differences in I were observed.

I was found to be elevated above the age trend for other nondiabetic subjects in 7 of 8 nondiabetic leukemic children dying shortly after treatment with ACTH. In the eighth subject ACTH therapy produced hyperglycemia and glycosuria and I was subnormal. The concentration of I at operation was low in the removed portions of pancreas from the 3 out of 4 children with unexplained hypoglycemia. It was low in 5 children dying with diarrhea, 4 dying in uremia, 2 dying after extended periods of under alimentation per se and in one child dying with glycogen storage disease.

In the 9 diabetic humans where the condition was discovered during the normal period of growth (growth-onset type), I was found to be very low relative to that for nondiabetic controls, but was much higher on the average in subjects who had passed the age when full stature is normally attained before the discovery of the diabetic condition (maturity-onset type). This difference is, in part at least, associated with the very low values for I found in diabetic coma due to the relatively high proportion of coma deaths in young diabetic subjects. Duration of the diabetic state had no demonstrable effect upon I in the maturity-onset type of subject.

In terms of islet-cell histology and extractable insulin of pancreas only the growth-onset type of

diabetes of human subjects was found to be comparable to the meta-diabetes of animals, including the experimental diabetes of dogs induced by anterior pituitary factors. The possibility was advanced that the characteristic atrophy of the islets of Langerhans' and very low values for the extractable insulin of pancreas at autopsy in growth-onset diabetes may be related to the simultaneous presence of hyperglycemia and growth factors.

MANAGEMENT OF DIABETES IN CHILDREN

A. L. CHUTE, M.D.

The management of diabetes in children revolves about 4 main subjects: (1) education, (2) diet, (3) insulin and (4) exercise.

Without intelligent co-operation and understanding on the part of the parent and the child, elaborate calculation of diet, and the careful regulation of insulin, are at best a wasted effort—at their worst, a false cloak of security.

The diet for a diabetic child must fulfill all the criteria for the diet of a normal child of the same age. It must be adequate in calories, minerals and vitamins, as well as in the essential elements of carbohydrate, fat and protein. The proportion of the latter in the diet should approximate those of any balanced nondiabetic diet.

In the Hospital for Sick Children, we use the proportion of 2 gm. of carbohydrate to 1 of fat and 0.9 of protein. Diets are most readily calculated according to age. We employ 5 main diets ranging from 1,430 calories for the 3 to 5 year olds to 2,450 calories for the 16 year olds. Each parent and child is fully trained in preparing the diet before they leave the hospital. To secure more nearly uniform blood sugar levels, 6 meals a day are customary. These consist of 3 main meals, breakfast, luncheon and dinner and 3 small lunches of 10 to 15 gm. of carbohydrate at midmorning, midafternoon and bedtime. Diabetic control is greatly facilitated if the food is weighed. However, older children should be taught to gauge portions and understand how to make suitable substitutions in order that occasional meals may be taken out with friends, or in restaurants without embarrassment or major loss of diabetic regulation.

In case of illness, of moderate severity, the total caloric intake is reduced to ⅔ of the normal amount, but the usual foods may be consumed. In serious illness a liquid diet is employed consisting chiefly of fruit juices and milk, equal to ⅔ of the usual caloric requirement. At camp or when the child is taking part in athletic activities, an increase in the diet is necessary, 200 to 400 calories a day may be required in addition to their normal intake.

Regulation of Insulin: Insulin is a necessity for all diabetic children. It should be employed just as soon as the diagnosis is established and must never be omitted. The knowledge of the types of insulin, in regard to time of onset, maximum effect and duration is essential for intelligent use. Briefly, unmodified or regular insulin has an onset of action in one hour; its maximum effect is reached in 4 hours and its duration is 8 hours. Protamine zinc insulin has a delay in its onset of reaction for approximately 6 hours. Its maximum effect occurs in 18 to 20 hours and the duration of action may be 36 hours or longer. Globin insulin has an onset of action in about 2 hours; a maximum effect in 8 hours; a duration of action of approximately 20 hours. NPH insulin has an onset of action in 2 hours, a maximum effect in 8 hours and a duration of action for 24 hours. One of the most satisfactory regimens in regard to insulin administration is to give both unmodified insulin and protamine zinc insulin in separate injections approximately 20 minutes before breakfast. In general ⅔ of the total dose is given as protamine zinc insulin and ⅓ as unmodified insulin.

Recently NPH insulin, a new form of protamine zinc insulin has been used. In more than 50% of diabetic children, satisfactory control can be obtained by this insulin alone. If necessary unmodified insulin may be added to form a mixture without loss of the rapid action of the unmodified insulin such as is seen when it is mixed with protamine zinc insulin.

Globin insulin gives results similar to NPH. As a general rule children under 5 years of age cannot be well adjusted to NPH insulin or globin insulin. Indeed, it should be emphasized that each patient requires individual study to determine the best insulin regimen and the most suitable dietary distribution, to bring about satisfactory regulation of his diabetic state. Rapid fluctuations from glycosuria to insulin reactions are frequent occurrences in children because diabetes is more labile in the young. In addition, variations in exercise and the frequency of infections upset the normal balance. To maintain reasonable control, the urine must be tested frequently—before each meal and at bedtime are ideal. However, in practice, a test before breakfast and one at 4 p.m. are useful guides.

The morning test indicates whether the long acting protamine zinc insulin is adequate, while the 4 p.m. test indicates whether enough of the quick acting unmodified insulin is being employed. Patients are taught to ignore occasional glycosuria; but glycosuria persisting for more than 2 to 3 days requires an increase in the insulin dosage. On the other hand, reactions occurring before lunch indicate an excess of unmodified insulin while nocturnal or early morning reactions are attributable to protamine zinc insulin. Such reactions require the reduction of the appropriate insulin. Mild reactions can be controlled with a teaspoonful of corn syrup, 2 lumps of sugar, or a piece of candy. If the child is unconscious the parents are instructed to give nothing by mouth, and to inject a ¼ to ½ cc. of epinephrine hydrochloride intramuscularly; if this is not effective a physician should inject 25 to 50 cc. of 50% glucose intravenously.

Diabetic coma is an emergency and if possible should be treated in the hospital with laboratory facilities. Unmodified insulin only should be used until acidosis and coma have been overcome. For infants, 5 units should be immediately given intramuscularly. Children of 1 to 5 years of age should receive 15 to 25 units; 5 to 10 years of age 25 to 50 units; and children 10 to 15, 50 to 75 units. If the patient is unconscious, a further dose equal to those already described should be given intravenously in addition to the intramuscular injection. Further dosage will depend on the response of the blood sugar which should be followed at 1 to 2 hour intervals until the blood sugar has returned to normal values. Intravenous fluids should be started as soon as possible. Hartmann's Ringer's lactate or normal saline are the most useful solutions. If, from the history, one suspects that the acidosis has been present for some time, and the CO_2 combining power is 15 vol. % or less, it is advisable to administer some form of alkali. To raise the CO_2 content, 1 vol. % may give 0.26 gm. of sodium bicarbonate/kg. body weight or 1.8 cc. of Sixth Molar Lactate/kg. body weight. Once the CO_2 combining power has risen to 25 vol. % or above, the further administration of fluids and sodium chloride solutions allows the kidney to regulate the acid base metabolism. Glucose solutions are usually not employed until the blood sugar has been brought to normal limits. Other methods of combating dehydration such as the intravenous administration of potassium, should be undertaken with a good deal of caution and it is usually best employed only in hospitals where laboratory facilities are available for measuring the concentration of these ions in the blood. Where laboratory facilities are not available for checking potassium levels the early use of broth and fruit juices by mouth is usually all that is necessary to supply the potassium requirement of the individual except in most severe cases.

Exercise plays a prominent part in the control of diabetes in children. Carbohydrate is burned with a greater economy of insulin during activity than at rest. Unaccustomed exercise by a diabetic patient receiving adequate insulin therefore may lead to an insulin reaction. In uncontrolled diabetes, on the other hand, exercise may cause increased fat utilization which in turn leads to ketosis and may lead to acidosis and possibly coma.

The psychologic management of diabetic children is immensely important. Summer camps are an excellent aid in solving many of their problems.

PROGNOSIS OF JUVENILE DIABETES

PRISCILLA WHITE, M.D.

Of 3,144 juvenile diabetic patients observed in the Joslin Clinic between 1898 and 1952, 875 might have survived 20 or more years of their disease. This number includes pre-insulin survivors as well as all patients who had onset of their diabetes between 1921 and 1931. Actually, of this number, 702, or 80%, achieved this length of life. Such survival is remarkable because the juvenile diabetic patient has the most virulent form of the disease and the child's normal rejection of the discipline and regimentation of diabetic treatment makes chemical control a difficult task.

In spite of these hazards, the specific functions of childhood, adolescence and adult life were for the most part completed. All except a few (1%) eventually grew and developed in satisfactory fashion. The number who attended college was greater than that of the general population. Of the 635 survivors in 1951, 90% were gainfully employed or carrying on useful lives. To the 139 males who reported their marriages, 156 children were born with 96% fetal survivals. One hundred ninety-five females reported marriages resulting in 289 pregnancies. One hundred ninety-seven of these reached viability with 75% fetal survival.

TABLE 1
STATUS AFTER 20 TO 24 YRS. DURATION OF DIABETES

Complication	Per Cent
Gangrene	2
Pulseless feet	11
Calcified arteries	88
Blindness	10
Proliferating retinitis	58
Nonproliferating retinitis	94
Cerebro-vascular accidents	4
Myocardial damage	18
Hypertension	40
Nephritis	37

Incidence of Vascular Disease and Freedom from It

Although physical, radiologic and postmortem examinations reveal in this group the great frequency of vascular lesions reported previously by us and others, an amazing number are free from incapacitating lesions after 20 years of their diabetes. The relative status is shown in table 1.

Evolution of Vascular Disease

The evolution of vascular disease in the juvenile diabetic patient shows the relatively early development and progressive inclusiveness of nonproliferating retinitis and calcification of arteries. The incidence of the nephropathies rises slowly to a peak and then tends to fall off. The level of blood pressure rises slowly and more constantly decade by decade.

Mortality

Of the 702 patients, 67, or 10%, died after 20 years. Vascular nephritis accounted for 63% of the deaths, coronary occlusion for 20 and miscellaneous causes for 17%.

Relation of Control of Diabetes to Vascular Lesions

In order to determine whether active diabetes influenced the frequency and severity of vascular lesions, the incidences of the more tangible evidences of poor control in the patients free from and in those who died from vascular disease were compared. The perfect group had infrequent evidence of severe ketoacidosis, hepatomegaly, hyperglycemia and hypercholesterolemia. The reverse was true of the patients who died from their vascular lesions. The relationship diabetic control, or the lack of it, bears to freedom from vascular lesions or disability as a result of them has been emphasized by Root and Wilson, by Jackson et al. and by Daeschner, Deisher and Hartman.

Prophylactic Measures for the Prevention of Arteriosclerosis

Immediate programs for control of vascular disease include the prescription for normal nutrition —adequate calories, high protein, controlled fat; quantities of insulin sufficient to the maintenance of the inactive diabetic state; correction of all infections and endocrine disturbances; wise use of rutin and, perhaps, sympathectomy as well as more complete education, better psychiatric handling and continuity of treatment.

Conclusions

Total absence of vascular disease occurred infrequently after 20 years of diabetes, but 8% only of the 702 twenty-year survivors died from their vascular lesions. Juvenile diabetic patients survive to more than middle age. Nearly all (over 90%) after 30 and after 25 years of diabetes were free from blindness, gangrene and cerebrovascular accidents. Two-thirds were free from the potentially incapacitating lesions proliferating retinitis and vascular nephritis. Vascular lesions did not appear to be dependent upon duration of diabetes alone. Poor control of diabetes paralleled both the degree and the frequency of the vascular lesions. Sepsis, too, appeared to be an important inciting factor. Some remedial measures have been attempted with apparent success. Despite the preponderance of vascular lesions after 20 years, they are not disabling in the majority of the cases. It is apparent that, just as lethal coma, lethal sepsis and lethal tuberculosis are no longer inevitable, lethal vascular disease can be averted or, at least, postponed.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

MATERNITY AND INFANT CARE FOR MILITARY DEPENDENTS

An Official Statement Adopted by the Executive Board AMERICAN PUBLIC HEALTH ASSOCIATION, INC.

DURING the early days of World War II families of Servicemen in the lowest pay grades found difficulty in securing medical care at the time of the birth of a new baby. Two primary factors contributed to this difficulty:

1. Insufficient financial resources of many men in lowest pay grades.
2. Inadequate facilities for care in certain areas where there were large concentrations of servicemen.

Such a state of affairs threatened the health of women and children. There also resulted an adverse effect on the morale of servicemen. At first local governmental agencies took action to remedy the situation; finally, the Emergency Maternity and Infant Care Program (EMIC) was established by the Federal government on a nationwide basis. This program was administered by State health agencies which received unmatched Federal funds through the Children's Bureau. These funds paid for maternity care (prenatal, delivery and postnatal), the care of any illness of the mother during the prenatal and postnatal period, and care of the infant (preventive and curative) during the first year of life. Wives and infants of men in the four lowest pay grades of the military services were eligible. During the total period of the war, over 1,200,000 mothers and 230,000 infants received service under the program. At its peak, about one-seventh of the total births in the United States were included, and every state and territory was covered.

This country has recently entered upon an indefinite and possibly long period of

military preparedness, during which time large numbers of young men will become members of the armed services. There is an increasing amount of discussion concerning possible Federal governmental assistance beyond that currently provided for the medical care of civilian dependents of military personnel. Proposals for such assistance are already before the Congress. The American Public Health Association believes that it is important to review the problem, in order to have available carefully considered recommendations that might facilitate the evaluation of any legislative proposals for governmental assistance.

Two broad questions are basic to the entire problem:

First, at what point in an increasing mobilization will some program of Federal assistance to the wives and children of men in the armed services become necessary?

Second, what form should it take?

Regarding the first question, it is clear that prediction of need at a specific future date is extremely difficult. However, certain items of information might serve as a basis for reaching a reasoned opinion as to whether a program was needed, or was likely to be needed at an early date. Such items as the following if kept up to date would be helpful in this respect:

The basic pay levels of the enlisted personnel by pay grades, including data concerning family and other special allowances. The number of enlisted men in each pay grade according to marital status and age.

The birth rate among married servicemen according to pay grade.

The number of requests for assistance, by type of request, made by enlisted personnel to the American Red Cross, to health and welfare departments and to similar agencies.

The number of enlisted men by pay grades and location whose wives are living away from their usual place of abode in order to be with their husbands.*

The amount and kind of medical care for civilian dependents which is being rendered or paid for by the armed forces.*

Even without such specific information, certain general recommendations may be made on the basis of experience in World War II and a knowledge of various factors in the current situation. It seems likely that as the program for military preparedness develops the need for Federal assistance will first be urgently felt in the same area of medical care as before, namely, in the area of maternity and infant care.

Therefore, this Association considers that the following are basic principles that should be used in evaluating any proposals for furnishing Federal assistance in this area. The program developed should:

1. Provide for the ready acceptance of all who apply and are eligible for service, particularly for non-residents and for those who started getting service in another state.
2. Assure a high quality of medical care including the services of physicians, nurses and related personnel as well as hospitalization.
3. Protect the physician-patient relationship, provide for free choice of physician; require a minimum amount of paper work; provide adequate and fair compensation for services, and protect the freedom and initiative of physicians and medical institutions.
4. Be designed to support the national effort during the emergency.
5. Be the most economical consistent with high quality of care.

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* Such items as the last two might be obtained by inserting questions in the routine Attitude Survey Studies which are conducted by the armed services.

Care might be provided in a number of ways, of which the following represent four possibilities: an expansion of military medical service for civilian dependents; a program of cash payments; a revised EMIC; and a program administered solely through existing non-profit insurance agencies, such as Blue Cross and Blue Shield.

According to present regulations, all civilian dependents of enlisted personnel may receive complete medical care from the armed service involved if the commanding officer of the hospital or other facility which might render the care deems the facility adequate. The overloading of such facilities by civilians may lead to building up medical military forces to an extent that would be undesirable, since such a process might easily remove too many doctors, nurses, and allied personnel from the community. Therefore the American Public Health Association seriously questions the wisdom of having military authorities responsible for the administration of a large medical program for civilians and does so not only because of the danger of overdevelopment, but also because such a trend is counter to sound community health organization for civilians.

Furthermore, this Association is of the opinion that any proposal which involves direct cash payments to the family for the purchase of medical care is unsound. Such a form of payment has the advantage of simple administration for cases involving the care of uncomplicated pregnancies, for cases of well-defined illnesses, and even for certain items of health supervision such as immunization. The disadvantages, however, outweigh the advantages. There is no assurance that the money will be used for paying medical or hospital expenses. Even when so used, there is no assurance of care from licensed physicians or hospitalization which meets even minimum standards. Such assurance is the basic requirement of a program designed to prevent lowering of present levels of service and to avoid interruption of health care for mothers and children. Furthermore, for the morale of servicemen to be maintained, they must be certain that their families have health protection rather than extra cash. A cash payment must be limited in amount to prevent skyrocketing charges. Payment in cash does not guarantee that additional charges will not be made. General health supervision of the infant is likely to be inadequately covered. Finally, with a system of cash payments it is very difficult to write and administer legislation which would provide for unusual complications or extraordinary costs. The importance of this to morale is obvious.

The EMIC of World War II had many good features from both the professional and lay point of view. The program had the advantages that it emphasized good standards of medical care and operated within the framework of existing community organization. In general, hospitals and doctors provided service to EMIC patients in the way they provided it to their other patients. EMIC assured complete care, regardless of complications or duration of illness. Many mothers, particularly the younger, ever-on-the-move group, found it very helpful to be able to deal, when necessary, with one agency, the Health Department, which in turn was usually able to direct them to community resources available to them. In complicated cases this was particularly helpful to the mother. On the other hand, there were justifiable complaints. While EMIC made allowance for variations in costs of hospital care, no satisfactory arrangement was found for making similar allowance for geographical variation in usual professional fees. Physicians, particularly in urban areas, felt fees were too low. Some states set up cumbersome and wasteful authorization procedures and reporting methods. The infant care provisions were but meagerly used, many babies being "lost" as far as well baby supervision was concerned.

One important development of recent years introduces a new factor that should be carefully considered in any thinking about this problem. This is the rapid growth of hospital insurance plans and the smaller but significant growth of insurance for physicians' services. The Blue Cross plans, for example, may offer possibilities for utilization because of their relatively advanced development. This applies especially to those which render service instead of paying cash indemnities. The feasibility of such a policy should be thoroughly explored. This approach would deserve serious consideration if a nation-wide uniform contract could be written providing quantitatively and qualitatively adequate service to the family dependents of members of the armed forces according to the standards set in this document. On the other hand, it is the opinion of this Association that a Blue Shield type of insurance for professional services would have to demonstrate its capacity for rapid and widespread distribution over the country and for more uniform scope of services covered before it should receive serious consideration. All non-profit insurance plans should be required to fulfill the qualitative and quantitative standards described below.

It is not the function of this Association to recommend a detailed program. The following specific recommendations are presented, however, as general guides which, in our view, would result in an improvement over the EMIC program of World War II.

1. The program should be set up by specific legislative act. This would provide a greater degree of stability.

2. Within reason, sufficient time should be allowed local governmental units to prepare for the program.

3. Sufficient administrative funds should be allowed to the Federal, state, and local groups that are to administer the program, and some of these funds should be available before the program is actually in operation.

4. Coverage should be governed by general need, but should include wives and infants of all enlisted men eligible for dependents' allowances and unmarried mothers and their infants when the father is an enlisted man and acknowledges paternity.

5. The care covered should be complete medical, nursing, and hospital care for the mother during pregnancy, labor and the postpartum period up to six weeks following delivery, as well as medical, nursing, and hospital care for the infant, including health supervision, during the first two years of life.

6. The program should be administered through the Children's Bureau and State health departments on the basis of plans submitted by the State health departments.

7. A national advisory council should be set up to advise, consult with and make recommendations to the administrator of the program. Such a council should be composed of a large group of persons (about 16-20) who can adequately represent the professional groups concerned, the interests of the individuals eligible for benefits, those administering service on the state level, and the public. They should elect their own chairman, set up their own agenda, meet on call of their chairman or the administrator at least annually, and their recommendations should be publicized. Each member of the advisory council should receive compensation for services rendered.

8. State plans should foster a high quality of care through:

a. Including only hospitals which meet specified standards as set by the State health agency.

b. Promoting preventive care, particularly of children, with allowance made fo:

payment of service in publicly supported programs such as child health conferences, as well as in the office of the private physician or in the hospital clinic.

c. Experimenting with ways of following the mother and baby to help assure that the child gets care.

d. Providing for an advisory committee composed of lay and professional representatives with power to elect its own chairman, set up its own agenda, and report and advise on the administration of the state program.

9. There should be enough flexibility to allow states to experiment with different ways of providing the service through non-profit insurance plans so long as these insurance plans provide appropriate remuneration for doctors and hospitals, and the same scope and quality of services specified by the overall plan.

10. State plans should foster ready transfer of patients and services on a regional basis within a state if such transfer will assist in taking the load off an overburdened area or in making additional services (particularly those of the medical consultant) available to the clients who live where they are not available.

11. State plans should fulfill the five principles enumerated on page 509.

TRENDS

By John P. Hubbard, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

PRACTICE OF PREVENTIVE PEDIATRIC CARE

A QUESTION which repeatedly arises in planning for broader distribution of health services for children is the extent to which health supervision is assumed to be a function of practicing physicians on the one hand and of official health agencies on the other hand. At the time of the Academy's study of child health services, about 90% of the health supervision given to the preschool child was attributable to general practitioners and pediatricians in private practice and only about 10% given in well child conferences. It was also observed that the amount of health supervision was distinctly less in areas of low economic status than in the more favored areas.

Since the Academy's study was completed additional evidence has been brought to light which corroborates the dominant role of the practicing physician in preventive medical care of infants and which again cites the discrepancy in both quantity and quality of care for the children of the less favored families.* By the use of fairly simple sampling technics, a study was conducted by Kandle and Goetz in one metropolitan center to determine the extent of immunization against diphtheria. This study, although limited to one city and one small fraction of health services for infants, indicates a trend which is important to those who, as teachers or practitioners, are responsible for child health.

Among the group of infants in the sample, the net level of immunization against diphtheria was 63% among white children and 41% among Negro children. In interpreting these data, the greater prevalence of diphtheria among whites should be taken into account.

It is unsound to compare studies conducted by different technics at different times on different population groups. Nevertheless, it is interesting to note that in the more recent study by Kandle and Goetz, 86% of white children who had been immunized against diphtheria had received this service from their private physicians as compared with only 15% of Negro children. Conversely, 58% of Negro children were immunized in health centers and only 8.5% of white children. Similar results were found in respect to smallpox vaccination and also for routine health examinations for infants. Thus, in general, white infants received extensive preventive services primarily from their own physicians while Negro babies received much less both in quantity and quality and the services were provided in the latter case primarily by health centers and hospitals.

When a comparison was made between the health protection for white infants of families in favorable circumstances and white infants of less favorable circumstances, the level of protection against diphtheria was significantly higher among the more prosperous group. There was no difference between the less advantaged white group and the Negro infants.

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* Kandle, R. P., and Goetz, H., "A Practical Method of Securing Data Regarding Services to Mothers and Infants," Am. J. Pub. Health **39**:1451 (November) 1949.

The conclusion reached by the authors is quoted as follows:

"In the city studied by this method, white mothers and their infants received extensive preventive medical services, primarily from their own doctors, while Negro mothers and their infants received much less both in quality and quantity, and it was provided mostly by health centers and hospitals. Securing high levels of the basic preventive services of immunization and medical antepartum care and medical supervision of infants seemed to depend chiefly upon the ability of the people to secure private physicians."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

CURRENT STATUS OF BIRTH, DEATH AND INFANT MORTALITY RATES

ON THE basis of provisional data it appears that infant mortality in the United States has continued to improve in 1951, despite the fact that the birth rate has gone up again. The National Office of Vital Statistics, Public Health Service, has published in the Monthly Vital Statistics Bulletin for February 1952 an analysis of the telegraphic reports received from the various states for the year 1951. While the data are subject to correction

MONTHLY VITAL STATISTICS BULLETIN

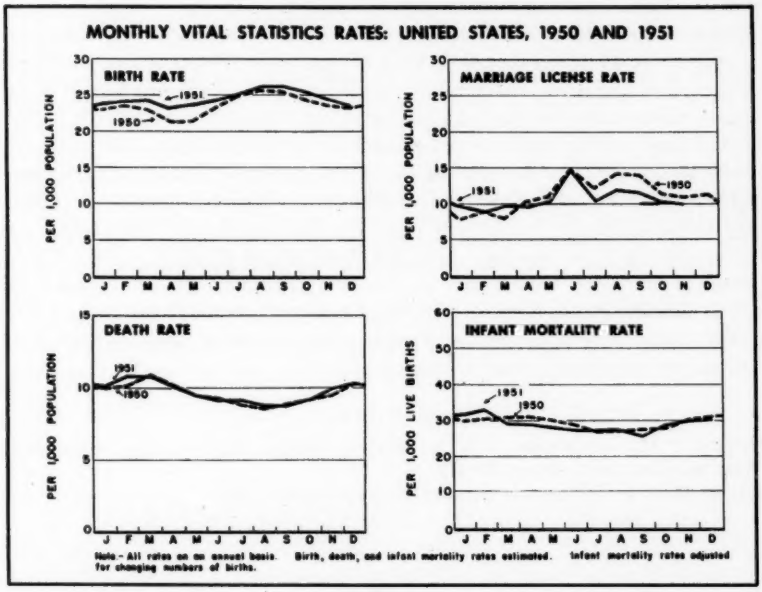
MONTHLY VITAL STATISTICS RATES: UNITED STATES, 1950 AND 1951
BIRTH RATE
MARRIAGE LICENSE RATE
DEATH RATE
INFANT MORTALITY RATE
PER 1,000 POPULATION
PER 1,000 LIVE BIRTHS
1951
1950
J F M A M J J A S O N D
Note - All rates on an annual basis. Birth, death, and infant mortality rates estimated. Infant mortality rates adjusted for changing numbers of births.

FIGURE 1

and final figures will almost surely result in slight revisions, previous experience indicates that the general trend is quite accurate.

Figure 1 presents the month by month comparison, throughout the year, for birth rate, death rate, and infant mortality rate. Marriage license rate is shown through November 1951. It will be noted that in every month of the year the birth rate was higher than in the corresponding month of 1950. The annual rate was 24.5 per 1000 population,

4.3% higher than in 1950 but 5% lower than the peak birth rate reached in 1947. Taking into account an estimate for births which were not reported it is thought that 3,833,000 births took place in 1951. This is the greatest number of births in one year in the history of our country. The increasing size of the problem of providing child health supervision for these infants will give food for thought to the pediatric profession.

The death rate was variable through the year but approximated 1952 figures quite closely. For the whole year the estimated rate was 9.7, compared with 9.6 for 1950. It is the fourth consecutive year in which the death rate has been lower than 10 per 1000 population.

Infant mortality started off in the first two months of the year with rates slightly higher than in 1950 and it appeared that there might be a setback to the uninterrupted decline which has been in evidence in the past 15 years. During the rest of the year, however, the rate dropped consistently and by the end of the year the estimated total rate, 28.8 per 1000 live births, was lower than the rate of 29.2 for 1950, establishing a new low record. It should be noted that the figures have been adjusted for the changing number of births since statisticians recognize that in an era of rising birth rate the crude figures may indicate a spuriously low infant mortality rate.[1] Marriages appear to be declining slightly since the rate for the first 11 months of 1951, 9.9, was 8% lower than the rate for 1950. The effect of this decline on the birth rate will be felt next year.

The downward trend in infant mortality rate since the first compilation of accurate national statistics in 1915 has been little short of spectacular.[2] Furthermore, the decline in the latter half of this period has been even more rapid than in the first half. It is difficult to assign specific reasons for this but a number of developments since the early 1930's may be cited. Fellows of the Academy will recall that it was founded in 1930 and promptly embarked on activities "to improve the health and welfare of our children, to raise the standards of pediatric education and practice, and to encourage research in pediatrics." Striking medical advances, particularly regarding diarrheal disease, other infections and care of newborn infants, have been registered. Enactment of the maternal and child health provisions of the Social Security Act resulted in a great extension of preventive health services to children. All of these, as well as general improvement in the sanitary environment, have contributed to the decline. Further progress is to be looked for confidently if professional and community efforts are maintained.

REFERENCES

1. Moriyama, I. M., and Greville, T. N. E., Effect of changing birth rates upon infant mortality, Vital Statistics, Special Deports **19**:399, 1944.
2. Wegman, M. E., Trends in infant mortality, PEDIATRICS **6**:673, 1950.

CORRESPONDENCE

MY DEAR DR. MCCULLOCH:

As examiner in pediatrics for the National Board of Medical Examiners, I would like to bring to the attention of the pediatricians an important change in Part III of the examination, as it involves pediatrics. This is the oral examination given at the end of a year's internship by "subsidiary boards" in 29 medical centers throughout the country. The clinical nature of the examination provides an opportunity to determine the candidate's ability to apply the knowledge which he has previously demonstrated in the written examination of Parts I and II.

For many years the examination has included medicine, surgery, and obstetrics as major subjects, while pediatrics has been included in a group of specialties as being of minor importance. The examination has been revised and pediatrics has been placed with the major subjects where it belongs. In the revised form an oral bedside examination will be given during one full day. Two hours are assigned to medicine and two hours to surgery, and one hour to pediatrics and one hour to obstetrics.

It is expected that approximately 1500 candidates will take the examination in June in the various centers. If each examiner examines 6 hours (6 candidates) on the day of the examination it will require 500 examiners in medicine and in surgery, and 250 in pediatrics and in obstetrics. While the men in the other three groups are accustomed to the examination it is a new experience for pediatricians. The number of examiners needed at each center will depend on the number of candidates presenting themselves for the examination at the particular center. All details as to time, place, and who will be asked to assist in the examination, are in the hands of the local subsidiary board at the center.

It further means that the wards of the children's hospitals, and children's wards in general hospitals, must be used to obtain material for the purpose of bedside examination. Previously the examination has not called for the use of patients in the pediatric examination.

As many pediatricians are aware it has taken years of continuing effort to have pediatrics recognized as one of the four major branches of clinical medicine. It was not until the mid-thirties that pediatrics was given a separate examination by the National Board of Medical Examiners in Part II of their examination. Now that the place of pediatrics has been fully recognized, it becomes the responsibility of the pediatricians, and the children's hospital services, in the various centers to cooperate fully and wholeheartedly with the local subsidiary boards in the centers where the examinations will be held.

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NEWS AND ANNOUNCEMENTS

The creation of a Bureau for Handicapped Children and the designation of Dr. Helen M. Wallace as Director of the new Bureau has been announced by the Department of Health, City of New York.

At present the program of the Bureau for Handicapped Children involves 6 different services for handicapped youngsters. It maintains a register of all children with orthopedic handicaps; it administers (at a cost of approximately $1,000,000 a year) the state aid program under which approved hospitals and convalescent centers are paid for the care of handicapped children; operates 29 diagnostic clinics chiefly for school age children; works with the Board of Education in placing children with handicaps in special classes; jointly, with the Board of Education and private organizations operates 2 special school units for youngsters with cerebral palsy and cooperates with the New York Heart Association and New York University in a special pilot program for children with rheumatic fever and heart disease.